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(54) Title: PHARMACEUTICAL COMPOUNDS

(57) Abstract: The invention provides novel inhibitors of protein tyrosine phosphatase sulfenyl amide and their use in medicine, for example in the treatment or prevention of disease states such as cancer, diabetes, rheumatoid arthritis and hypertension. Also provided are novel crystal structures and the use of the crystal structures and their X-ray coordinates in the development of new drugs.

PHARMACEUTICAL COMPOUNDS

This invention relates to novel inhibitors of protein tyrosine phosphatase (PTP) activity, to a novel PTP form and crystal structures thereof, and to the uses of the crystal structures and novel form intermediate in the design of new drug molecules. The invention also provides the use of the inhibitors in medicine and in particular the treatment of disease states mediated by PTP activity, and to pharmaceutical compositions containing the compounds.

Background of the Invention

Protein tyrosine phosphatases (PTPs) are crucial in regulating signal transduction pathways involving tyrosine phosphorylation[1] and have been implicated in cancer, diabetes, rheumatoid arthritis, and hypertension[2].

Protein tyrosine phosphorylation plays a major role in regulation of many cell functions including response to hormones, growth factors and cytokines as well as in cell proliferation and apoptosis. Protein tyrosine phosphatases (PTPases) therefore represent an important control point in these regulatory mechanisms. Atypical tyrosine phosphorylation of specific proteins or components of signal transduction pathways has been implicated in a variety of human diseases including diabetes (diabetes type I and II) obesity, autoimmune diseases, acute and chronic inflammation, osteoporosis, proliferative disorders including various forms of cancer, growth disorders, response to infection and defective platelet aggregation. Such atypical tyrosine phosphorylation can result from dysregulation of both the kinases and or phosphatases controlling the process. In many cases PTPase activity is the major mechanism limiting the extent of phosphorylation and therefore such phosphatases represent key targets for therapeutic agents intended to exert pharmacological control over such processes.

Type 2 diabetes is characterized by abnormalities of insulin secretion and by insulin resistance of the major target tissues producing a diminished uptake and metabolism of glucose.

Protein-tyrosine phosphatases (PTPases) play a key role in the regulation of reversible tyrosine phosphorylation in the insulin action pathway. The receptor for insulin is an integral membrane protein with tyrosine kinase activity and insulin signal transduction is initiated by the phosphorylation of specific tyrosyl residues receptor. This initiates a complex signalling cascade leading to the phosphorylation of several key substrates including the IRS proteins on specific tyrosine residues. These activation steps are balanced, in turn, by specific cellular PTPases that dephosphorylate and inactivate the receptor kinase and reverse the adapter function of the receptor substrate proteins. PTP1B is a key component of this network and levels of PTP1B have been reported to be increased in diabetes associated with insulin resistance. Inhibition of PTP1B would therefore be expected to increase the strength of the signal initiated by the insulin resceptor and reverse the insulin resistance in such patients.

Other cellular responses dependent on the action of tyrosine kinases are similarly dependent on the phosphatases which limit the strength of the response. For example the growth factors EGF, VEGf and PDGF all initiate a network of signalling cascades dependent on tyrosine phosphorylation by their specific receptor tyrosine kinases. The response of lymphocytes to specific antigen activation and of other immune cells to cytokines such as IL-6 also use non-receptor tyrosine kinases as key components in their signal transduction pathways. Therefore inhibition of other members of the PTP family would be expected to control cell growth, cellular transformation, tumor formation, lymphocyte activation, cell migration, and inflammatory responses.

PTP1B belongs to a large family of PTPs characterised by an 11 residue signature sequence (I/V)HCXAGXXR(S/T)G which includes the catalytic cysteine (Cys215)[1,10]. Its catalytic mechanism involves a nucleophilic attack by Cys215 on a phosphotyrosine substrate resulting in a covalent phosphocysteine intermediate, which is subsequently hydrolysed by an activated water molecule[11]. The crystal structure of PTP1B shows that the PTP signature motif adopts a cradle-like conformation forming the base of the active site (figure 1a)[12]. Its backbone amide atoms point to the centre of the cradle, which together with the invariant Arg221

provides an excellent environment to stabilise the negatively charged Cys215 side chain and bind the phosphate moiety of an incoming substrate[13] (figure 1a). A hydrogen bond between the hydroxyl group of Ser222 and the sulphur atom of Cys215 further stabilises the cysteine conformation and helps to maintain its reduced pKa (~5.4)[14]. One side of the active site is flanked by the so-called WPD-loop, which adopts an open conformation in the unliganded enzyme and closes over a bound phosphotyrosine residue[13]. The opposite side is formed by the phosphotyrosine (pTyr) recognition loop containing Tyr46, which mainly determines specificity for phosphotyrosine substrates (figure 1a)[15].

Increasing literature evidence suggests that the cellular redox state is involved in regulating PTP activity by reversibly oxidizing their catalytic cysteines. Current literature describes the role of the sulfenic acids (Cys-SOH)[3-6]. Further oxidation to the sulfinic (Cys-SO_2H) and sulfonic (Cys-SO_3H) forms causes irreversible inhibition.

Further, there are examples of sulphur-nitrogen bonds in the literature. The reaction of a sulfenic acid derivative of glyceraldehyde-3-phosphate dehydrogenase with the small molecule, benzylamine, to form a sulfenamide has been reported by Allison *et al* [26].

Reich *et al.* [27] has described studies involving the formation of cyclic selenenamide structure in a small molecule model system and suggested that in its oxidized form mammalian glutathione peroxidase, a selenoenzyme, may have a cyclic selenenamide structure.

Summary of the Invention

The Applicants have found that oxidation of the catalytic cysteine at the active site of PTP by oxidants leads to the formation of a sulfenyl amide moiety at the active site. The 'sulfenyl amide' is an isothiazolidin-3-one ring system, which has not been previously observed in proteins. The sulfenyl amide moiety is believed to be a protective intermediate in the oxidative inhibition of PTPs that prevents further irreversible oxidation to sulfinic and sulfonic acids. Formation of the sulfenyl

amide moiety at the active site leads to a loss of the enzyme's catalytic activity. Reduction of the sulfenyl amide moiety with a physiological reducing agent such as glutathione leads to regeneration of the active form of the enzyme.

This invention is based in part on recognition that compounds that stabilize the sulfenyl amide form or effect reversible or irreversible covalent modification of the sulfenyl amide form will be useful as therapeutic agents. Thus, by preventing or inhibiting the reversion of the inactive or less active sulfenyl amide form to the active form of PTP, the overall level of activity of PTP within a cellular environment can be substantially reduced.

Accordingly, the invention provides compounds that inhibit reversion of the PTP sulfenyl amide to the active form of PTP and their use in therapy.

Also covered by the invention are cysteine-containing proteins which have a suitably nucleophilic cysteine in the active site to facilitate formation of the sulfenyl amide. This includes phosphatases and phosphatase-like proteins which are structurally homologous to the PTPs such as rhodanese and bacterial phosphotransferases e.g. IIBcel (also known as IIBchb).

The term "cysteine-containing proteins" includes all proteins characterised by the HC(X5)R signature motif and other proteins belonging and related to this family, for example, those that have a remnant of this motif capable of adopting a conformation similar to the PTP phosphate binding cradle and which have a catalytic cysteine. A preferred set of proteins is the set in which there is an active site cysteine and an unusually polarised peptide bond between the active site cysteine and the following residue, in particular those with the HC(X5)R signature motif. One hypothesis is that in the HC(X5)R signature motif this bond is polarised by the conserved His in the signature motif. The HC(X5)R phosphatase family includes classical PTPs as well as the more distantly related low molecular weight (LMW) phosphatases, dual specificity phosphatases and rhodanese/CDC25 superfamily. A preferred subset is the set of those cysteine-containing proteins that do not have more than one cysteine in the active site.

PTPs of the invention characterised by the above structural motif include all PTPs. In a preferred aspect of the invention this refers to PTPs without a second active site cysteine in close proximity of the catalytic cysteine, and more preferably those PTPs with one cysteine residue in the binding site. Preferred PTPs are PTPs characterised by the 11 residue signature sequence (I/V)HCXAGXXR(S/T)G. Preferred PTPs include LAR, T-cell PTP, PTP-α and PTP1b, more preferably PTP1b.

The sulfenyl amide form of PTB1B has been prepared by the Applicants under controlled conditions and its structure determined by X-ray diffraction analysis. The structural data can be used in methods of rational drug design to provide compounds that inhibit reversion of the PTP sulfenyl amide to the active form of PTP.

Although the invention is specifically illustrated herein by reference to PTP1B, it is considered to be applicable also to other PTPs where the cellular redox state is involved in regulating PTP activity by reversibly oxidizing their catalytic cysteines to form sulfenyl amides. The terms "protein tyrosine phosphatase sulfenyl amide", "PTP sulfenyl amide" and "sulfenyl amide" used herein refer generally to PTPs in which a cysteine moiety at the catalytic site has been oxidized to form a sulfenyl amide, unless the context indicates otherwise. For the avoidance of doubt, it is noted that the terms "protein tyrosine phosphatase sulfenyl amide", "sulfenyl amide protein tyrosine phosphatase", "PTP sulfenyl amide" and "sulfenyl amide PTP" as used herein are interchangeable and refer to the same entity unless the context requires otherwise.

The various aspects and embodiments of the invention are described in more detail below and defined in the claims appended hereto.

Brief Description of the Drawings

Figure 1 provides a comparison of the structures of native and sulfenyl-amide PTP1B.

Figure 1a is a ribbon diagram of PTP1B showing the phosphate-binding cradle, the WPD-loop and the pTyr recognition loop.

Figure 1b shows the superimposition of the structure of native PTP1B (light grey) and the sulfenyl-amide containing structure (dark grey) showing the different conformations of the pTyr recognition loop and the phosphate-binding cradle.

Figure 1c shows the electron density of the novel sulfenyl-amide derivative and its neighbouring residues. The electron density map in Figure 1c is contoured at 1σ. All figures are generated using Aesop (Martin Noble, unpublished).

Figure 2 shows a putative mechanism of sulfenyl-amide formation and subsequent reactivation. As illustrated, the catalytic cysteine of PTP1B (E-SH) is oxidised to a sulfenic acid (E-S-OH). The sulfenyl-amide may be formed by a direct mechanism involving a nucleophilic attack of the backbone nitrogen of Ser216 on the Sγ atom of Cys215 and subsequent release of water. Alternatively the sulfenic acid may be oxidised to a highly reactive intermediate by an oxidising agent e.g. by peroxide e.g. H_2O_2[24, 25] or an oxidised thiol, which then reacts to give the sulfenyl-amide. Reactivation of the enzyme occurs via mixed disulfide formation with a thiol. R, denotes glutathione or DTT, X the leaving groups OOH (sulfenoperoxoic acid) or OS(O)R (sulfinothioic acid).

Figure 3 illustrates the different oxidation states of the catalytic cysteine. The structures shown are the sulfonic (A), sulfinic (B) and sulfenic acid derivatives (C) of Cys215. The phosphate-binding cradle comprising residues 215 to 222 is shown in ball-and-stick representation. Hydrogen bonds are shown as dashed lines. The maps are contoured at 3σ and in all maps the peaks are higher than 5σ.

Detailed Description of the Invention

The PTP sulfenyl amides of the invention

In one aspect, the present invention contemplates an isolated PTP sulfenyl amide. The sulfenyl amides of the invention have a variety of uses, as described herein.

The terms "PTP sulfenyl amide", "sulfenyl amide PTP" and (in the context of PTP) "sulfenyl amide" alone are used herein as generic terms to define any PTP (as defined below) in which a cysteine moiety at the catalytic site is oxidized to form a sulfenyl amide.

The term "PTP" is used generally herein (and in particular in the context of the PTP sulfenyl amides of the invention) as a generic term to include all members of the PTP protein family, whether natural, synthetic or recombinant. Preferred are PTPs without a second active site cysteine in close proximity to the catalytic cysteine, and more particularly preferred are those PTPs with only one cysteine residue in the binding site. Such preferred PTPs include LAR, T-cell PTP, PTP-α and PTP1B (the latter specifically exemplified herein).

The term "PTP" is also intended to encompass PTP homologues, analogues, allelic forms, species variants, derivatives, muteins or equivalents, whether natural, synthetic or recombinant (as hereinbelow defined).

The term "homologue" is used herein in two distinct senses. It is used *sensu stricto* to define proteins that share a common ancestor to the PTP. In this sense it covers orthologues (species variants which have diverged in different organisms following a speciation event) and paralogues (variants which have diverged within the same organism after a gene duplication event). Thus, there is a direct evolutionary relationship between the PTP and such homologues and this may be reflected in structural and/or functional similarities. For example, orthologues may perform the same role in each organism in which they are found, while paralogues may perform functionally related (but distinct) roles within the same organism.

The term is also used herein *sensu lato* to define a PTP which is to some extent structurally similar (i.e. not necessarily evolutionary related and/or structurally and functionally equivalent) to a given (reference) PTP (for example, to any one of LAR, T-cell PTP, PTP-α and PTP1B). In this sense, homology is recognised on the basis of purely structural criteria by the presence of amino acid sequence identities

and/or conservative amino acid changes and/or similar secondary, tertiary or quaternary structures.

In this context, a conservative amino acid substitution is one in which the amino acid residue is replaced with an amino acid residue having a similar side chain. Families of amino acid residues having similar side chains have been defined in the art (as set out for example by Dayhoff *et alia*, Atlas of protein structure vol. 5, National BioMed Fd'n, Washington D.C., 1979). These families include amino acids with basic side chains (e. g., lysine, arginine, histidine), acidic side chains (e.g. aspartic acid, glutamic acid), non-charged polar side chains (e. g. glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine), non-polar side chains (e. g. alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (e. g. threonine, valine, isoleucine), and aromatic side chains (e. g. tyrosine, phenylalanine, tryptophan, histidine).

The homologues of the invention therefore include proteins having at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90% or 95% sequence identity with the reference PTP, and include truncated forms of naturally-occurring PTP proteins. Such truncates are preferably at least 25%, 35%, 50% or 75% of the length of the corresponding wild-type PTP and may have at least 50%, 55%, 60% or 65% sequence identity (more preferably, at least 70%, 75%, 80%, 85%, 90% or 95% sequence identity) with that wild-type PTP. Particularly preferred homologues are truncates that contain a segment preferably comprising at least 8, 15, 20 or 30 contiguous amino acids that share at least 75%, 80%, 85%, 90% or 95% sequence identity with that reference PTP.

Preferred truncates for PTP1b are residues 1-321 or residues 1-298 of the reference wild-type sequence. A particularly preferred truncate for PTP1b is the one defined by residues 1-321 of reference PTP1b sequence accession number P18031 [SwissProt: PTN1_HUMAN].

For the avoidance of doubt, full length sulfenyl amide wild-type PTPs are within the scope of the invention as well as truncated versions of sulfenyl amide wild-type PTPs.

For the purposes of the invention, homologues may also be recognised as those proteins the corresponding DNAs of which are capable of specifically or selectively cross-hybridising, or which can cross-hybridise under selective, appropriate and/or appropriately stringent hybridisation conditions.

The term "selectively or specifically (cross)hybridisable" in this context indicates that the sequences of the corresponding ssDNAs are such that binding to a unique (or small class) of homologous sequences can be obtained under more or less stringent hybridisation conditions. Exemplary stringent conditions can be found in, for example, Current Protocols in Molecular Biology, John Wiley & Sons, N. Y. (1989), 6.3.1-6.3.6. A preferred, non-limiting example of stringent hybridization conditions is hybridization in 6x sodium chloride/sodium citrate (SSC) at about 45°C, followed by one or more washes in 0.2x SSC, 0.1 SDS at a temperature of from about 50°C to 65°C.

The term "allelic form" is used herein to define a naturally-occurring alternative form (allelic variant) of a wild-type PTP sequence which reflects naturally-occurring differences in the PTP gene pool. Allelic forms may be isolated and identified by making suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source from individuals of the appropriate species.

The term "analogue" is used herein to define proteins with similar functions and/or structures and which are not necessarily evolutionarily related. PTP analogues which share function but which have no or little structural similarities are likely to have arisen by convergent evolution. Conversely, PTP analogues which share structural similarities but which exhibit few or no functional similarities are likely to have arisen by divergent evolution. PTP analogues may be identified, for example, by screening a library of proteins to detect those with similar function(s)

but different physical properties, or by screening for proteins which share structural features but not necessarily any functions (e.g. by immunological screening).

The term "species variant" is used herein to define the corresponding PTP from a different organism. Thus, species variants share a direct evolutionary relationship.

Species variants may be isolated and identified by making suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source from the desired species. Preferably, species variants are those isolated from mammalian species. Most preferably, species variants are those isolated from certain mammalian species such as, for example, Pan troglodytes, Gorilla gorilla, Pongo pygmaeus, Hylobates concolor, Macaca mulatta, Papio papio, Papio hamadryas, Cercopithecus aethiops, Cebus capucinus, Aotus trivirgatus, Sanguinus oedipus, Microcebus murinus, Mus musculus, Rattus norvegicus, Cricetulus griseus, Felis catus, Mustela vison, Canis familiaris, Oryctolagus cuniculus, Bos taurus, Ovis aries, Sus scrofa, and Equus caballus, for which genetic maps have been created allowing the identification of syntenic relationships between the genomic organization of genes in one species and the genomic organization of the related genes in another species (O'Brien and Seuanez, 1988, Ann. Rev. Genet. 22 : 323-351 ; O'Brien et al., 1993, Nature Genetics 3: 103-112; Johansson et al., 1995, Genomics 25: 682-690; Lyons et al., 1997, Nature Genetics 15: 47-56; O'Brien et al., 1997, Trends in Genetics 13 (10): 393-399; Carver and Stubbs, 1997, GenomeResearch7 : 1123-1137; all of which are incorporated by reference herein).

The term "derivative" as applied herein to the PTPs of the invention is used to define PTPs which are modified versions of any wild-type or truncated PTP. Such derivatives may include fusion proteins, in which the proteins of the invention have been fused to one or more different proteins, peptides or amino acid tags (for example an antibody or a protein domain conferring a biochemical activity, to act as a label, or to facilitate purification). Particularly preferred are derivatives in which the PTP proteins or peptides are modified by a polyHis (6xHis) tag to facilitate

purification of the peptide derivative on Ni^{2+} agarose beads. It is further preferred that the proteins are derivatives of truncated PTP proteins.

The derivatives may also be products of synthetic processes that use a wild-type PTP as a starting material or reactant.

The term "mutein" is used herein to define PTPs that are mutant forms of a wild-type PTP, i.e. PTP proteins in which one or more amino acids have been added, altered, deleted, replaced, inserted or substituted. The muteins of the invention therefore include fragments, truncates and fusion peptides (e.g. comprising fused immunoglobulin, receptor, tag, label or enzyme moieties).

The muteins of the invention therefore include truncated forms of a wild-type PTP. Such truncates are preferably least 25%, 35%, 50% or 75% of the length of the corresponding wild-type PTP and may have at least 65% sequence identity (more preferably, at least 70%, 75%, 80%, 85%, 90% or 95% sequence identity) with that PTP.

The muteins of the invention also include PTPs in which mutations have been introduced which effectively promote or impair one or more activities of the PTP, for example mutations which promote or impair the function of the active site.

Muteins may be produced by any convenient method. Conveniently, site-directed mutagenesis with mutagenic oligonucleotides may be employed using a double stranded template (pBluescript KS II construct containing a PTP gene), (e.g. Chameleon'M or QuikChange'M - Stratagene'M). After verifying each mutant derivative by sequencing, the mutated gene is excised and inserted into a suitable vector so that the modified protein can be over-expressed and purified.

Preferred mutant forms are truncates consisting (or consisting essentially) of the PTP 11-residue signature sequence described herein. Particularly preferred are truncates that contain a segment preferably comprising at least 8, 15, 20 or 30

contiguous amino acids that share at least 75%, 80%, 85%, 90% or 95% sequence identity with the PTP from which they are derived by truncation.

The term "equivalent" is used herein to define those PTP analogues which exhibit substantially the same function(s) and which share at least some structural features (e.g. functional domains), but which have not evolved from a common ancestor. Such equivalents are typically synthetic proteins (see below) and may be generated, for example, by identifying sequences of functional importance (e.g. by identifying conserved or canonical sequences, functional domains or by mutagenesis followed by functional assay), selecting an amino acid sequence on that basis and then synthesising a peptide based on the selected amino acid sequence. Such synthesis can be achieved by any of many different methods known in the art, including solid phase peptide synthesis (to generate synthetic peptides) and the assembly (and subsequent cloning) of oligonucleotides. Some synthetic protein analogues may be chimaeras, and such equivalents can be designed and assembled for example by concatenation of two or more different structural and/or functional peptide domains from different proteins using recombinant DNA techniques.

The homologues, analogues, fragments, muteins, equivalents or derivatives of the PTPs of the invention may also be defined *inter alia* as those proteins which cross-react with antibodies to one or more wild-type PTPs, and in particular those which cross-react with antibodies directed against a PTP lacking a second active site cysteine in close proximity of the catalytic cysteine (for example a PTP with only one cysteine residue in the binding site). Thus, the homologues, fragments, muteins, equivalents or derivatives of the PTPs of the invention include proteins which cross-react with antibodies to one or more of LAR, T-cell PTP, PTP-α and PTP1B.

For the purposes of the present invention, sequence identity is determined by comparing the amino acid sequences of the protein when aligned so as to maximize overlap and identity while minimizing sequence gaps. In particular, sequence identity may be determined using any of a number of mathematical algorithms. A nonlimiting example of a mathematical algorithm used for comparison of two

sequences is the algorithm of Karlin and Altschul (1990) Proc. Natl. Acad. Sci. USA 87: 2264-2268, modified as in Karlin and Altschul (1993) Proc. Natl. Acad. Sci. USA 90: 5873-5877.

Another example of a mathematical algorithm used for comparison of sequences is the algorithm of Myers and Miller (1988) CABIOS 4: 11-17. Such an algorithm is incorporated into the ALIGN program (version 2.0) which is part of the GCG sequence alignment software package. When utilizing the ALIGN program for comparing amino acid sequences, a PAM120 weight residue table, a gap length penalty of 12, and a gap penalty of 4 can be used. Yet another useful algorithm for identifying regions of local sequence similarity and alignment is the FASTA algorithm as described in Pearson and Lipman (1988) Proc. Natl. Acad. Sci. USA 85: 2444-2448.

Preferred for use according to the present invention is the WU-BLAST (Washington University BLAST) version 2.0 software. WU-BLAST version 2.0 executable programs for several UNIX platforms can be downloaded from ftp ://blast. wustl. edu/blast/executables. This program is based on WU-BLAST version 1.4, which in turn is based on the public domain NCBI-BLAST version 1.4 (Altschul and Gish, 1996, Local alignment statistics, Doolittle ed., Methods in Enzymology 266: 460-480; Altschul et al., 1990, Basic local alignment search tool, Journal of Molecular Biology 215: 403-410; Gish and States, 1993, Identification of protein coding regions by database similarity search, Nature Genetics 3: 266-272; Karlin and Altschul, 1993, Applications and statistics for multiple high-scoring segments in molecular sequences, Proc. Natl. Acad. Sci. USA 90: 5873-5877; all of which are incorporated by reference herein).

In all search programs in the suite the gapped alignment routines are integral to the database search itself. Gapping can be turned off if desired. The default penalty (Q) for a gap of length one is Q=9 for proteins and BLASTP, and Q=10 for BLASTN, but may be changed to any integer. The default per-residue penalty for extending a gap (R) is R=2 for proteins and BLASTP, and R=10 for BLASTN, but may be

changed to any integer. Any combination of values for Q and R can be used in order to align sequences so as to maximize overlap and identity while minimizing sequence gaps. The default amino acid comparison matrix is BLOSUM62, but other amino acid comparison matrices such as PAM can be utilized.

The term "isolated" is used herein to indicate that the PTP sulfenyl amide exists in a physical milieu distinct from that in which it occurs in nature. For example, the isolated sulfenyl amide may be substantially isolated with respect to the complex cellular milieu in which it naturally occurs. The absolute level of purity is not critical, and those skilled in the art can readily determine appropriate levels of purity according to the use to which the PTP sulfenyl amide is to be put. The term "isolating" when used a step in a process is to be interpreted accordingly.

In many circumstances, the isolated PTP sulfenyl amide will form part of a composition, for example a more or less crude extract containing many other molecules and substances, buffer systems, matrices or excipients, which may for example contain other components (including assay reagents and proteins, such as albumin).

In other circumstances, the isolated PTP sulfenyl amide may be purified to essential homogeneity, for example as determined by PAGE or column chromatography (for example HPLC or mass spectrometry). In preferred embodiments, the isolated PTP sulfenyl amide is essentially the sole protein in a given composition.

The isolated PTP sulfenyl amide of the invention may be crystallized. Crystals of the isolated PTP sulfenyl amide find particular utility in some applications of the invention (for example, for the *in silico* analyses described below).

The PTP sulfenyl amides of the invention need not be isolated in the sense defined above, however. For example, more or less crude preparations derived from spent media used to culture host cells expressing PNP or PNP sulfenyl amide may be

used. Such supernatants may be treated in various ways, for example by oxidation, concentration, filtration, centrifugation, spray drying, dialysis and/or lyophilisation.

The term "natural" is used herein to define a PTP that has been derived from a naturally-occurring wild-type protein source by chemical or enzymic treatment. Naturally occurring PTPs may be obtained by purification (e.g. by column chromatography) from cellular material in which the native PTP is expressed.

The term "synthetic PTP" is used herein to define a PTP that has been chemically synthesised *in vitro* (for example by any of the commercially available solid-phase peptide-synthesis systems).

The term "recombinant" is used herein to define a PTP that has been produced by that body of techniques collectively known as "recombinant DNA technology".

Thus, although this invention is based (at least in part) on the identification and characterization of a novel sulfenyl amide intermediate arising from oxidation of a cysteine moiety at the active site of PTP1B (see below), any of a large number of different PTP sulfenyl amides are contemplated by the invention and each finds general application in the various methods and processes described herein.

Use of the PTP sulfenyl amides of the invention *per se* in Drug Discovery

The PTP sulfenyl amides of the invention may be used *inter alia* in various drug screening processes.

For example, the invention provides a process for screening for a PTP inhibitor comprising the steps of: (a) providing the PTP sulfenyl amide (or a homologue, allelic form, species variant, derivative or mutein thereof); (b) contacting the sulfenyl amide of step (a) with a test compound; and (c) determining whether the test compound binds to the sulfenyl amide.

The screening processes of the invention as described above are preferably high throughput processes. The screens identify and/or select compounds with PTP

sulfenyl amide binding activity. Such compounds are candidate PTP modulators, and can be subjected to further analysis and/or screening in order to determine their activity as therapeutic agents (see for example the section headed "Assays for Screening for Active Compounds", below). Alternatively, or in addition, they may be crystallized with PTP1B sulfenyl amide (e.g. by co-crystallization or by soaking) for X-ray analysis. The resulting X-ray structure may be compared with that of Table 1 or Table 2 for a variety of purposes.

For example, the PTP sulfenyl amides of the invention may be used in a process for producing a PTP inhibitor comprising the steps of: (a) providing a PTP sulfenyl amide (or a homologue, allelic form, species variant, derivative or mutein thereof); (b) contacting the sulfenyl amide of step (a) with a test compound; (c) determining whether the test compound binds to the sulfenyl amide; and (d) identifying the test compound as a PTP inhibitor on the basis of its ability to prevent or inhibit the reductive activation of the PTP sulfenyl amide to active PTP.

In such processes, at least two chemically distinct test compounds may be identified in step (d) and the process may then further comprise the step of linking two or more of the chemically distinct compounds to produce a multimeric PTP inhibitor. Such processes embody the linked fragment approaches described in more detail in the section headed "Linked fragment and fragment growing approaches", below.

The PTP sulfenyl amides of the invention may therefore be used in a process for producing a pharmaceutical composition comprising the steps of: (a) providing a PTP sulfenyl amide (or a homologue, allelic form, species variant, derivative or mutein thereof); (b) contacting the sulfenyl amide of step (a) with a test compound; (c) determining whether the test compound binds to the sulfenyl amide; (d) identifying the test compound as a PTP inhibitor on the basis of its ability to prevent or inhibit the reductive activation of the PTP sulfenyl amide to active PTP; and (e) incorporating the inhibitor identified in step (d) into a pharmaceutical excipient.

The invention contemplates PTP inhibitors, drugs and pharmaceutical compositions obtainable by, or obtained by, the process of the invention described above.

Identification and Characterization of the Three Dimensional Structure of Sulfenyl Amide PTP

This invention is based on the identification and characterization of a novel sulfenyl amide intermediate arising from oxidation of a cysteine moiety at the active site of a protein tyrosine phosphatase.

The catalytic domain (residues 1-321) of PTP1B was expressed in *E. coli* cells according to known procedures and was purified and crystallized. The oxidation state of the catalytic cysteine of PTP1B was probed by means of soaking experiments using various oxidizing agents and crystal structures were subsequently obtained for a novel sulfenyl-amide intermediate of PTP1B, as well as sulfenic, sulfinic and sulfonic PTP1B derivatives.

Soaking crystals of the catalytic domain of PTB1B with 2-phenyl-isoxazolidine-3,5-dione gave rise to a modified crystal structure (the PTP1B sulfenyl amide), the structure for which has been determined by X-ray diffraction analysis. Atomic coordinates of the catalytic domain are set out in Table 1 and Table 2.

Accordingly, in one aspect, the invention provides a crystal of sulfenyl amide protein tyrosine phosphatase 1B.

Crystals

In another aspect, the invention provides a crystal of sulfenyl amide protein tyrosine phosphatase 1B having a Unit cell dimensions: a = 87.686 Å, b = 87.686 Å, c = 103.721 Å, $\alpha = 90.00°$, $\beta = 90.00°$, $\gamma = 120.00°$ and a space group: $P3_1\,2\,1$. Unit cell variability of 5% may be observed in all dimensions.

The invention also provides a crystal of sulfenyl amide protein tyrosine phosphatase 1B having a resolution better than, i.e. numerically lower than, 3.0 Å, preferably lower than 2.6 Å.

The invention also provides crystals of sulfenyl amide protein tyrosine phosphatase 1B capable of being soaked with compound(s) to form co-complex structures.

Table 1 coordinates

The invention also provides a crystal of sulfenyl amide protein tyrosine phosphatase 1B having the structure defined by the coordinates of Table 1.

Table 1 gives atomic coordinate data for sulfenyl amide protein tyrosine phosphatase 1B. In Table 1 the third column denotes the atom type, the fourth the residue type, the fifth the chain identification, the sixth the residue number. The seventh, eighth and ninth columns are the X, Y, Z coordinates respectively of the atom in question, the tenth column defines the occupancy of the atom, the eleventh column gives the temperature factor of the atom.

Table 2 coordinates

The invention further provides a crystal of sulfenyl amide protein tyrosine phosphatase 1B having the structure defined by the coordinates of Table 2.

The coordinates of Table 2 are defined as the coordinates of Table 1 as amended in the manner outlined in Table 2. Table 2 varies in six ways from Table 1. These changes do not affect the positioning of the atoms of sulfenyl amide protein tyrosine phosphatase 1B. The co-ordinates of Table 2 represent the same spatial distribution of atoms of sulfenyl amide protein tyrosine phosphatase 1B as contained in Table 1 but in a format consistent with that of the EBI Macromolecular Structure Database (Hinxton, UK). Thus, the invention covers all co-ordinate files that essentially represent the same spatial distribution of sulfenyl amide protein tyrosine phosphatase 1B atoms independent of file format.

The coordinates of Table 1 or Table 2 provide a measure of atomic location in Angstroms, to a third decimal place. The coordinates are a relative set of positions that define a shape in three dimensions, so it is possible that an entirely different set of coordinates having a different origin and/or axes could define a similar or identical shape. Furthermore, varying the relative atomic positions of the atoms of the structure so that the root mean square deviation of the residue backbone atoms

(i.e. the nitrogen-carbon-carbon backbone atoms of the protein amino acid residues) or the C-alpha atoms is less than 1.5 Å (preferably less than 1.0 Å, more preferably less than 0.5 Å and even more preferably less than 0.47 Å) when superimposed on the coordinates provided in Table 1 or Table 2 for the residue backbone atoms, will generally result in a structure which is substantially the same as the structure of Table 1 or Table 2 in terms of both its structural characteristics and potency for structure-based design of PTP1B inhibitors.

Likewise changing the number and/or positions of the water molecules and/or substrate molecules of Table 1 or Table 2 will not generally affect the potency of the structure for structure-based design of PTP1B inhibitors. Thus for the purposes described herein as being aspects of the present invention, it is within the scope of the invention if: the Table 1 or Table 2 coordinates are transposed to a different origin and/or axes; the relative atomic positions of the atoms of the structure are varied so that the root mean square deviation of residue backbone atoms or the C-alpha atoms is less than 1.5 Å (preferably less than 1.0 Å , more preferably less than 0.5 Å and even more preferably less than 0.47 Å) when superimposed on the coordinates provided in Table 1 or Table 2 for the residue backbone atoms; and/or the number and/or positions of water molecules and/or substrate molecules is varied. References herein to the coordinate data of Table 1 or Table 2 thus include the coordinate data in which one or more individual values of the Tables are varied in this way. By "root mean square deviation" we mean the square root of the arithmetic mean of the squares of the deviations from the mean.

It is also within the scope of the invention if the coordinate file represents the same spatial distribution of sulfenyl amide protein tyrosine phosphatase 1B atoms but in a different file format. Alternative file formats (e.g. such as a format consistent with that of the EBI Macromolecular Structure Database (Hinxton, UK)) which may include a different ordering of these atoms, or a different designation of the residues or residue molecule atoms, may be used or preferred by others of skill in the art. However it will be apparent that the use of a different file format to present or manipulate the coordinates of the Tables is within the scope of the present invention. Thus for the purposes described herein as being aspects of the present

invention, it is within the scope of the invention if the coordinates are essentially the same as Table 1 or Table 2, essentially comprise the coordinates of Table 1 or Table 2, or are a set of coordinates that materially correspond to those of Table 1 or Table 2.

Other crystals of the invention include crystals which have selected coordinates of the binding pocket, wherein the amino acid residues associated with those selected coordinates are located in a protein framework which holds these amino acids in a relative spatial configuration corresponding to the spatial configuration of those amino acids in Table 1 or Table 2. By "corresponding to", it is meant within an r.m.s.d. of less than 2.0 Å, preferably less than 1.5 Å, more preferably less than 1.0 Å, even more preferably less than 0.5Å and most preferably less than 0.47 Å. In a further embodiment it is it within an r.m.s.d. of less than 0.3 Å, less than 0.25 Å, or less than 0.2 Å, and most preferably less than 0.1 Å. The amino acids which provide the selected coordinates are preferably selected from amino acids which form part of at least one sulfenyl amide protein tyrosine phosphatase 1B binding cavity, where these are residues 1 to 56 as described herein or combinations thereof as defined further herein below.

Those of skill in the art will appreciate that in many applications of the invention, it is not necessary to utilise all the coordinates of Table 1 or Table 2, but merely a portion of them. For example, as described below, in methods of modelling candidate compounds with PTP sulfenyl amide, selected coordinates of PTP sulfenyl amide may be used, for example at least 5, preferably at least 10, more preferably at least 20 and even more preferably at least 100 atoms of the sulfenyl amide structure. Likewise, the other applications of the invention described herein, including homology modelling and structure solution, and data storage and computer assisted manipulation of the coordinates, may also utilise all or a portion of the coordinates of Table 1 or Table 2. A preferred aspect of the invention is where the portion of the coordinates relates to the selected coordinates of the binding pocket. The amino acids which provide the selected coordinates are preferably selected from amino acids which form part of at least one sulfenyl amide

protein tyrosine phosphatase 1B binding cavity, where these are residues 1 to 56 as described herein or combinations thereof as defined further herein below.

It will also be appreciated that the invention also includes within its scope crystals of PTP sulfenyl amide comprising amino acids having the atomic coordinates of Tables 1 or 2, but wherein the crystal comprises further amino acids in addition to those for which the coordinates are given. Therefore, unless explicitly set out to the contrary, or otherwise made clear from the context, references throughout the present specification to the use of all or selected coordinates of or from Tables 1 or 2 does not exclude the use of additional coordinates due to the presence of further amino acids.

Comparison of protein structures

Protein structure similarity is routinely expressed and measured by the root mean square deviation (r.m.s.d.), which measures the difference in positioning in space between two sets of atoms. The r.m.s.d. measures distance between equivalent atoms after their optimal superposition. The r.m.s.d. can be calculated over all atoms, over residue backbone atoms (i.e. the nitrogen-carbon-carbon backbone atoms of the protein amino acid residues), main chain atoms only (i.e. the nitrogen-carbon-oxygen-carbon backbone atoms of the protein amino acid residues), side chain atoms only or more usually over C-alpha atoms only. For the purposes of this invention, the r.m.s.d. can be calculated over any of these, using any of the methods outlined below.

Methods of comparing protein structures are discussed in Methods of Enzymology, vol. 115, pg 397-420. The necessary least-squares algebra to calculate r.m.s.d. has been given by Rossman and Argos (J. Biol. Chem. , vol. 250, pp7525 (1975)) although faster methods have been described by Kabsch (Acta Crystallogr., Section A, A92, 922 (1976); Acta Cryst. A34, 827-828 (1978)), Hendrickson (Acta Crystallogr., Section A, A35, 158 (1979)); McLachan (J. Mol. Biol., vol 128, pp49 (1979) and Kearsley (Acta Crystallogr., Section A, A45, 208 (1989)). Some algorithms use an iterative procedure in which the one molecule is moved relative to the other, such as that described by Ferro and Hermans (Ferro and Hermans, Acta

Crystallographic, A33, 345-347 (1977)). Other methods, e.g. Kabsch's algorithm, locate the best fit directly.

Programs for determining r.m.s.d include MNYFIT (part of a collection of programs called COMPOSER, Sutcliffe, M.J., Haneef, I., Carney, D. and Blundell, T.L. (1987) Protein Engineering, 1, 377-384), MAPS (Lu, G. An Approach for Multiple Alignment of Protein Structures (1998, in manuscript and on http://bioinfo1.mbfys.lu.se/TOP/maps.html)).

It is usual to consider C-alpha atoms and the r.m.s.d. can then be calculated using programs such as LSQKAB (Collaborative Computational Project 4. The CCP4 Suite: Programs for Protein Crystallography, *Acta Crystallographica*, D50, (1994), 760-763), QUANTA (commercially available from Accelrys, San Diego, CA), Insight (commercially available from Accelrys, San Diego, CA), Sybyl® (commercially available from Tripos, Inc., St Louis), O (Jones et al., *Acta Crystallographica*, A47, (1991), 110-119), and other coordinate fitting programs.

In, for example, the programs LSQKAB and O, the user can define the residues in the two proteins that are to be paired for the purpose of the calculation. Alternatively, the pairing of residues can be determined by generating a sequence alignment of the two proteins, programs for sequence alignment are discussed in more detail above. The atomic coordinates can then be superimposed according to this alignment and an r.m.s.d. value calculated. The program Sequoia (C.M. Bruns, I. Hubatsch, M. Ridderström, B. Mannervik, and J.A. Tainer (1999) Human Glutathione Transferase A4-4 Crystal Structures and Mutagenesis Reveal the Basis of High Catalytic Efficiency with Toxic Lipid Peroxidation Products, *Journal of Molecular Biology* 288(3): 427-439) performs the alignment of homologous protein sequences, and the superposition of homologous protein atomic coordinates. Once aligned, the r.m.s.d. can be calculated using programs detailed above. For sequences identical, or highly identical, the structural alignment of proteins can be done manually or automatically as outlined above. Another approach would be to generate a superposition of protein atomic coordinates without considering the sequence.

It is more normal when comparing significantly different sets of coordinates to calculate the r.m.s.d. value over C-alpha atoms only. It is particularly useful when analysing side chain movement to calculate the r.m.s.d. over all atoms and this can be done using LSQKAB and other programs.

Mutants

Also, modifications in the sulfenyl amide protein tyrosine phosphatase 1B crystal structure due to e.g. mutations, additions, substitutions, and/or deletions of amino acid residues could account for variations in the atomic coordinates. However, atomic coordinate data of sulfenyl amide protein tyrosine phosphatase 1B modified so that a ligand that bound to one or more binding sites of sulfenyl amide protein tyrosine phosphatase 1B would be expected to bind to the corresponding binding sites of the modified sulfenyl amide protein tyrosine phosphatase 1B are, for the purposes described herein as being aspects of the present invention, also within the scope of the invention. References herein to the coordinates of Table 1 or Table 2 thus include the coordinates modified in this way. Preferably, the modified coordinate data define at least one sulfenyl amide protein tyrosine phosphatase 1B binding cavity.

Crystals of the invention also include crystals of sulfenyl amide protein tyrosine phosphatase 1B mutants. In addition, sulfenyl amide protein tyrosine phosphatase 1B mutants may be crystallized in co-complex with known sulfenyl amide protein tyrosine phosphatase 1B substrates or inhibitors or novel compounds.

As explained herein, a mutant sulfenyl amide protein tyrosine phosphatase 1B is a sulfenyl amide protein tyrosine phosphatase 1B protein characterized by the replacement or deletion of at least one amino acid from the wild type PTP1B. Such a mutant may be prepared for example by site-specific mutagenesis, or incorporation of natural or unnatural amino acids.

As explained herein, the present invention therefore contemplates sulfenyl amide protein tyrosine phosphatase 1B mutants as hereinbefore defined.

For example, the sulfenyl amide protein tyrosine phosphatase 1B mutants may define a polypeptide which is obtained by replacing at least one amino acid residue in a native or synthetic sulfenyl amide protein tyrosine phosphatase 1B with a different amino acid residue and/or by adding and/or deleting amino acid residues within the native polypeptide or at the N- and/or C-terminus of a polypeptide corresponding to sulfenyl amide protein tyrosine phosphatase 1B, and which has substantially the same three-dimensional structure as sulfenyl amide protein tyrosine phosphatase 1B from which it is derived. By having substantially the same three-dimensional structure is meant having a set of atomic structure co-ordinates that have a root mean square deviation (r.m.s.d.) of less than or equal to about 1.5 Å, preferably less than 0.47 Å, when superimposed with the atomic structure co-ordinates of the sulfenyl amide protein tyrosine phosphatase 1B from which the mutant is derived when at least about 50% to 100% of the C_α atoms of the sulfenyl amide protein tyrosine phosphatase 1B are included in the superposition. A mutant may have, but need not have, enzymatic or catalytic activity.

To produce homologues or mutants, amino acids present in the said protein can be replaced by other amino acids having similar properties, for example hydrophobicity, hydrophobic moment, antigenicity, propensity to form or break α-helical or β-sheet structures, and so. Substitutional variants of a protein are those in which at least one amino acid in the protein sequence has been removed and a different residue inserted in its place. Amino acid substitutions are typically of single residues but may be clustered depending on functional constraints e.g. at a crystal contact. Preferably amino acid substitutions will comprise conservative amino acid substitutions. Insertional amino acid variants are those in which one or more amino acids are introduced. This can be amino-terminal and/or carboxy-terminal fusion as well as intrasequence. Examples of amino-terminal and/or carboxy-terminal fusions are affinity tags, MBP tag, and epitope tags.

Amino acid substitutions, deletions and additions that do not significantly interfere with the three-dimensional structure of the sulfenyl amide protein tyrosine

phosphatase 1B will depend, in part, on the region of the sulfenyl amide protein tyrosine phosphatase 1B where the substitution, addition or deletion occurs. In highly variable regions of the molecule, non-conservative substitutions as well as conservative substitutions may be tolerated without significantly disrupting the three-dimensional structure of the molecule. In highly conserved regions, or regions containing significant secondary structure, conservative amino acid substitutions are preferred.

As explained earlier, conservative amino acid substitutions are well known in the art, and include substitutions made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity and/or the amphipathic nature of the amino acid residues involved. For example, negatively charged amino acids include aspartic acid and glutamic acid; positively charged amino acids include lysine and arginine; amino acids with uncharged polar head groups having similar hydrophilicity values include the following: leucine, isoleucine, valine; glycine, alanine; asparagine, glutamine; serine, threonine; phenylalanine, tyrosine. Other conservative amino acid substitutions are well known in the art.

In some instances, it may be particularly advantageous or convenient to substitute, delete and/or add amino acid residues to a sulfenyl amide protein tyrosine phosphatase 1B binding pocket or catalytic residue in order to provide convenient cloning sites in the cDNA encoding the polypeptide, to aid in purification of the polypeptide, to modify compound binding etc. Such substitutions, deletions and/or additions which do not substantially alter the three dimensional structure of sulfenyl amide protein tyrosine phosphatase 1B will be apparent to those having skills in the art.

It should be noted that the mutants contemplated herein need not exhibit enzymatic activity. Indeed, amino acid substitutions, additions or deletions that interfere with the catalytic activity of the protein tyrosine phosphatase 1B but which do not significantly alter the three-dimensional structure of the catalytic region are specifically contemplated by the invention. Such crystalline polypeptides, or the

atomic structure co-ordinates obtained there from, can be used to identify compounds that bind to the protein.

The crystallization of such mutants and the determination of the three-dimensional structures by X-ray crystallography rely on the ability of the mutant proteins to yield crystals that diffract at high resolution. The mutant protein could then be used to obtain information on compound binding through the determination of mutant protein/ligand complex structures, which may be characterized using the sulfenyl amide protein tyrosine phosphatase 1B crystal structure of Table 1 or Table 2.

The mutations can be introduced by site-directed mutagenesis e.g. using a Stratagene QuikChange™ Site-Directed Mutagenesis Kit or cassette mutagenesis methods (see e.g. Ausubel et al., eds., *Current Protocols in Molecular Biology*, John Wiley & Sons, Inc., New York, and Sambrook et al., *Molecular Cloning: a Laboratory Manual*, 2nd ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, (1989)).

To the extent that the present invention relates to sulfenyl amide protein tyrosine phosphatase 1B -ligand complexes and mutant and homologue proteins of sulfenyl amide protein tyrosine phosphatase 1B, crystals of such proteins may be formed. The skilled person would recognize that the conditions provided herein for crystallizing sulfenyl amide protein tyrosine phosphatase 1B may be used to form such crystals. Alternatively, the skilled person would use the conditions as a basis for identifying modified conditions for forming the crystals.

Thus the aspects of the invention relating to crystals of sulfenyl amide protein tyrosine phosphatase 1B, may be extended to crystals of a mutant, analogue or homologue, or mutein

Homology Modelling

The invention also provides a means for homology modelling of other proteins (referred to below as target sulfenyl amide protein tyrosine phosphatase proteins).

By "homology modelling", it is meant the prediction of related sulfenyl amide protein tyrosine phosphatase structures based either on X-ray crystallographic data or computer-assisted *de novo* prediction of structure, based upon manipulation of the coordinate data of Table 1 or Table 2.

"Homology modeling" extends to target sulfenyl amide protein tyrosine phosphatase proteins, which are analogues or homologues of the sulfenyl amide protein tyrosine phosphatase 1B protein whose structure has been determined in the accompanying examples.

The term "homologous regions" describes amino acid residues in two sequences that are identical or have similar (e.g. aliphatic, aromatic, polar, negatively charged, or positively charged) side-chain chemical groups. Identical and similar residues in homologous regions are sometimes described as being respectively "invariant" and "conserved" by those skilled in the art.

In general, the method involves comparing the amino acid sequences of the sulfenyl amide protein tyrosine phosphatase 1B protein of Table 1 or Table 2 with a target sulfenyl amide protein tyrosine phosphatase protein by aligning the amino acid sequences (Dunbrack et al., *Folding and Design*, 2, (1997), 27-42). Amino acids in the sequences are then compared and groups of amino acids that are homologous (conveniently referred to as "corresponding regions") are grouped together. This method detects conserved regions of the polypeptides and accounts for amino acid insertions or deletions.

Homology between amino acid sequences can be determined using commercially available algorithms. The programs *BLAST*, *GAPPED BLAST*, *BLASTN*, *PSI-BLAST* AND *BLAST 2* sequences (provided by the National Center for Biotechnology Information) are widely used in the art for this purpose, and can align homologous regions of two amino acid sequences. These may be used with default parameters to determine the degree of homology between the amino acid

sequence of the Table 1 or Table 2 protein and other target sulfenyl amide protein tyrosine phosphatase proteins, which are to be modeled.

Analogues are defined as proteins with similar three-dimensional structures and/or functions with little evidence of a common ancestor at a sequence level.

Homologues are defined as previously as proteins with evidence of a common ancestor, i.e. likely to be the result of evolutionary divergence and are divided into remote, medium and close sub-divisions based on the degree (usually expressed as a percentage) of sequence identity.

A homologue is defined here as a protein with at least 15% sequence identity or which has at least one functional domain, which is characteristic of sulfenyl amide protein tyrosine phosphatase 1B.

There are two types of homologue: orthologues and paralogues. Orthologues are defined as homologous genes in different organisms, i.e. the genes share a common ancestor coincident with the speciation event that generated them. Paralogues are defined as homologous genes in the same organism derived from a gene/chromosome/ genome duplication, i.e. the common ancestor of the genes occurred since the last speciation event.

The homologues could also be mutants as described above.

Once the amino acid sequences of the polypeptides with known and unknown structures are aligned, the structures of the conserved amino acids in a computer representation of the polypeptide with known structure are transferred to the corresponding amino acids of the polypeptide whose structure is unknown. For example, a tyrosine in the amino acid sequence of known structure may be replaced by a phenylalanine, the corresponding homologous amino acid in the amino acid sequence of unknown structure.

The structures of amino acids located in non-conserved regions may be assigned manually by using standard peptide geometries or by molecular simulation techniques, such as molecular dynamics. The final step in the process is accomplished by refining the entire structure using molecular dynamics and/or energy minimization.

Homology modeling as such is a technique that is well known to those skilled in the art (see e.g. Greer, *Science*, vol. 228, (1985), 1055, and Blundell *et al.*, *Eur. J. Biochem*, vol. 172, (1988), 513). The techniques described in these references, as well as other homology modeling techniques, generally available in the art, may be used in performing the present invention.

Thus the invention provides a method of homology modeling comprising the steps of: (a) aligning a representation of an amino acid sequence of a target sulfenyl amide protein tyrosine phosphatase protein of unknown three-dimensional structure with the amino acid sequence of the sulfenyl amide protein tyrosine phosphatase 1B of Table 1 or Table 2 to match homologous regions of the amino acid sequences; (b) modeling the structure of the matched homologous regions of said target sulfenyl amide protein tyrosine phosphatase of unknown structure on the corresponding regions of the sulfenyl amide protein tyrosine phosphatase 1B structure as defined by Table 1 or Table 2; and (c) determining a conformation (e.g. so that favorable interactions are formed within the target sulfenyl amide protein tyrosine phosphatase of unknown structure and/or so that a low energy conformation is formed) for said target sulfenyl amide protein tyrosine phosphatase of unknown structure which substantially preserves the structure of said matched homologous regions.

Preferably one or all of steps (a) to (c) are performed by computer modeling.

The aspects of the invention described herein which utilize the sulfenyl amide protein tyrosine phosphatase 1B structure *in silico* may be equally applied to homologue models of sulfenyl amide protein tyrosine phosphatase obtained by the

above aspect of the invention, and this application forms a further aspect of the present invention. Thus having determined a conformation of a sulfenyl amide protein tyrosine phosphatase by the method described above, such a conformation may be used in a computer-based method of rational drug design as described herein.

In a preferred aspect of this invention the co-ordinates are used to model the structure of target sulfenyl amide protein tyrosine phosphatases, particularly homologues of sulfenyl amide protein tyrosine phosphatase 1B, for example PTP-α, T-cell PTP, or LAR.

Structure solution

The structure of the human sulfenyl amide protein tyrosine phosphatase 1B can also be used to solve the crystal structure of other target sulfenyl amide protein tyrosine phosphatase proteins including other crystal forms of sulfenyl amide protein tyrosine phosphatase 1B, mutants, and co-complexes of sulfenyl amide protein tyrosine phosphatase 1B, where X-ray diffraction data or NMR spectroscopic data of these target sulfenyl amide protein tyrosine phosphatase proteins have been generated and require interpretation in order to provide a structure.

In the case of sulfenyl amide protein tyrosine phosphatase 1B, this protein may crystallize in more than one crystal form. The structure coordinates of sulfenyl amide protein tyrosine phosphatase 1B, or portions thereof, as provided by this invention are particularly useful to solve the structure of those other crystal forms of sulfenyl amide protein tyrosine phosphatase 1B. They may also be used to solve the structure of sulfenyl amide protein tyrosine phosphatase 1B mutants, sulfenyl amide protein tyrosine phosphatase 1B co-complexes, or the structure of the crystalline form of any other protein with significant amino acid sequence homology to sulfenyl amide protein tyrosine phosphatase 1B.

In the case of other target sulfenyl amide protein tyrosine phosphatase proteins, particularly the mutant sulfenyl amide protein tyrosine phosphatase proteins

referred to above, the present invention allows the structures of such targets to be obtained more readily where raw X-ray diffraction data are generated.

Thus, where X-ray crystallographic or NMR spectroscopic data are provided for a target sulfenyl amide protein tyrosine phosphatase 1B-ligand complex, or a sulfenyl amide protein tyrosine phosphatase 1B homologue or analogue of unknown three-dimensional structure, the structure of sulfenyl amide protein tyrosine phosphatase 1B, as defined by Table 1 or Table 2, may be used to interpret the data to provide a likely structure for the other sulfenyl amide protein tyrosine phosphatases by techniques which are well known in the art, e.g. phasing in the case of X-ray crystallography and assisting peak assignments in NMR spectra.

One method that may be employed for these purposes is molecular replacement. In this method, the unknown crystal structure, whether it is another crystal form of sulfenyl amide protein tyrosine phosphatase 1B, a sulfenyl amide protein tyrosine phosphatase 1B mutant, or a sulfenyl amide protein tyrosine phosphatase 1B co-complex, or the crystal of a target sulfenyl amide protein tyrosine phosphatase protein with amino acid sequence homology to protein tyrosine phosphatase 1B, may be determined using the sulfenyl amide protein tyrosine phosphatase 1B structure coordinates of this invention as provided herein. This method will provide an accurate structural form for the unknown crystal more quickly and efficiently than attempting to determine such information *ab initio*.

Examples of computer programs known in the art for performing molecular replacement are CNX (Brunger A.T.; Adams P.D.; Rice L.M., Current Opinion in Structural Biology, Volume 8, Issue 5, October 1998, Pages 606-611 (also commercially available from Accelrys San Diego, CA) or Amore (Navaza, J. (1994). Amore: An Automated Package for Molecular Replacement. Acta Cryst. A50, 157-163).

Thus, in a further aspect of the invention provides a method for determining the structure of a protein, which method comprises providing the co-ordinates of Table

1 or Table 2, and either (a) positioning the co-ordinates in the crystal unit cell of said protein so as to provide a structure for said protein or (b) assigning NMR spectra peaks of said protein by manipulating the coordinates of Table 1 or Table 2.

In a preferred aspect of this invention the co-ordinates are used to solve the structure of target sulfenyl amide protein tyrosine phosphatase, particularly homologues of sulfenyl amide protein tyrosine phosphatase 1B, for example PTP-α, T-cell PTP, or LAR.

Computer systems

In another aspect, the present invention provides systems, particularly a computer system, the systems containing either (a) atomic coordinate data according to Table 1 or Table 2, said data defining the three-dimensional structure of sulfenyl amide protein tyrosine phosphatase 1B or at least selected coordinates thereof; (b) structure factor data (where a structure factor comprises the amplitude and phase of the diffracted wave) for sulfenyl amide protein tyrosine phosphatase 1B, said structure factor data being derivable from the atomic coordinate data of Table 1 or Table 2; (c) atomic coordinate data of a target sulfenyl amide protein tyrosine phosphatase protein generated by homology of the target based on the data of Table 1 or Table 2; (d) atomic coordinate data of a target sulfenyl amide protein tyrosine phosphatase protein generated by interpreting X-ray crystallographic data or NMR data by reference to the data of Table 1 or Table 2; or (e) structure factor data derivable from the atomic coordinate data of (c) or (d).

For example the computer system may comprise: (i) a computer-readable data storage medium comprising data storage material encoded with the computer-readable data; (ii) a working memory for storing instructions for processing said computer-readable data; and (iii) a central-processing unit coupled to said working memory and to said computer-readable data storage medium for processing said computer-readable data and thereby generating structures and/or performing rational drug design. The computer system may further comprise a display coupled to said central-processing unit for displaying said structures.

The invention also provides such systems containing atomic coordinate data of target sulfenyl amide protein tyrosine phosphatase proteins wherein such data have been generated according to the methods of the invention described herein based on the starting data provided by Table 1 or Table 2.

Such data are useful for a number of purposes, including the generation of structures to analyze the mechanisms of action of sulfenyl amide protein tyrosine phosphatase 1B proteins and/or to perform rational drug design of compounds which interact with sulfenyl amide protein tyrosine phosphatase 1B, such as compounds which are inhibitors of sulfenyl amide protein tyrosine phosphatase 1B.

In another aspect, the invention provides a computer-readable storage medium, comprising a data storage material encoded with computer readable data, wherein the data are defined by all or a portion (e.g. selected coordinates as defined herein) of the structure coordinates of sulfenyl amide protein tyrosine phosphatase 1B of Table 1 or Table 2, or a homologue of sulfenyl amide protein tyrosine phosphatase 1B, wherein said homologue comprises backbone atoms that have a root mean square deviation from the backbone atoms (nitrogen-carbon$_\alpha$-carbon) of Table 1 or Table 2 of not more than 1.5 Å.

The invention also provides a computer-readable data storage medium comprising a data storage material encoded with a first set of computer-readable data comprising a Fourier Transform of at least a portion (e.g. selected coordinates as defined herein) of the structural coordinates for sulfenyl amide protein tyrosine phosphatase 1B according to Table 1 or Table 2; which, when combined with a second set of machine readable data comprising an X-ray diffraction pattern of a molecule or molecular complex of unknown structure, using a machine programmed with the instructions for using said first set of data and said second set of data, can determine at least a portion of the structure coordinates corresponding to the second set of machine readable data.

In a further aspect, the present invention provides computer readable media with at least one of: (a) atomic coordinate data according to Table 1 or Table 2 recorded thereon, said data defining the three-dimensional structure of sulfenyl amide protein tyrosine phosphatase 1B, or at least selected coordinates thereof; (b) structure factor data for sulfenyl amide protein tyrosine phosphatase 1B recorded thereon, the structure factor data being derivable from the atomic coordinate data of Table 1 or Table 2; (c) atomic coordinate data of a target sulfenyl amide protein tyrosine phosphatase protein generated by homology modeling of the target based on the data of Table 1 or Table 2; (d) atomic coordinate data of a sulfenyl amide protein tyrosine phosphatase 1B-ligand complex or a sulfenyl amide protein tyrosine phosphatase 1B homologue or analogue generated by interpreting X-ray crystallographic data or NMR data by reference to the data of Table 1 or Table 2; and (e) structure factor data derivable from the atomic coordinate data of (c) or (d).

By providing such computer readable media, the atomic coordinate data can be routinely accessed to model sulfenyl amide protein tyrosine phosphatase 1B or selected coordinates thereof. For example, Rasmol (Sayle et al., *TIBS*, vol. 20, (1995), 374) is a publicly available computer software package which allows access and analysis of atomic coordinate data for structure determination and/or rational drug design.

On the other hand, structure factor data, which are derivable from atomic coordinate data (see e.g. Blundell et al., in *Protein Crystallography*, Academic Press, New York, London and San Francisco, (1976)), are particularly useful for calculating e.g. difference Fourier electron density maps.

A further aspect of the invention provides a method of providing data for generating structures and/or performing rational drug design for sulfenyl amide protein tyrosine phosphatase 1B, sulfenyl amide protein tyrosine phosphatase 1B homologues or analogues, complexes of sulfenyl amide protein tyrosine phosphatase 1B with a candidate modulator, or complexes of sulfenyl amide protein

tyrosine phosphatase 1B homologues or analogues with candidate modulators, the method comprising:

(i) establishing communication with a remote device containing computer-readable data comprising at least one of: (a) atomic coordinate data according to Table 1 or Table 2, said data defining the three-dimensional structure of sulfenyl amide protein tyrosine phosphatase 1B, at least one sub-domain of the three-dimensional structure of sulfenyl amide protein tyrosine phosphatase 1B, or the coordinates of a portion of atoms of sulfenyl amide protein tyrosine phosphatase 1B; (b) structure factor data for sulfenyl amide protein tyrosine phosphatase 1B, said structure factor data being derivable from the atomic coordinate data of Table 1 or Table 2; (c) atomic coordinate data of a target sulfenyl amide protein tyrosine phosphatase 1B homologue or analogue generated by homology modeling of the target based on the data of Table 1 or Table 2; (d) atomic coordinate data of a protein generated by interpreting X-ray crystallographic data or NMR data by reference to the data of Table 1 or Table 2; and (e) structure factor data derivable from the atomic coordinate data of (c) or (d); and (ii) receiving said computer-readable data from said remote device.

Thus the remote device may comprise e.g. a computer system or computer readable media of one of the previous aspects of the invention. The device may be in a different country or jurisdiction from where the computer-readable data is received. The communication may be via the internet, intranet, e-mail etc. Typically the communication will be electronic in nature, but some or all of the communication pathway may be optical, for example, over optical fibre transmission lines.

Drug Discovery

Determination of the 3D structure of PTP1B provides important information about the nature of the changes to the active site of PTPs upon oxidation, in particular the changes in PTP1B upon oxidation to the PTP1B sulfenyl amide. In particular, the X-ray data provide information about new binding sites created by distortion of the active site as a consequence of the formation of the sulfenyl amide. Information about the new binding sites can then be used for rational design of compounds that

bind to PTPsulfenyl amide, especially PTP1B sulfenyl amide. This can be achieved by e.g. computational techniques which identify possible binding ligands for the active sites, by enabling linked-fragment approaches to drug design, and by enabling the identification and location of bound ligands using X-ray crystallographic analysis. These techniques are discussed in more detail below.

In silico Analysis

The provision of the crystal structure of PTP1B sulfenyl amide allows a novel approach for drug discovery for modulators of this inactive form of PTP and in particular of PTP1B. Accordingly, the invention provides a computer-based method of rational drug design which comprises:

providing the structure of the PTP1b sulfenyl amide as defined by the coordinates of Table 1 or Table 2;

providing the structure of a candidate modulator molecule; and

fitting the structure of candidate to the structure of the sulfenyl amide of Table 1 or Table 2.

More particularly, the crystal structure of the sulfenyl amide can be used to design drug molecules that bind to the sulfenyl amide of PTP1B to inhibit or prevent its conversion to the active form of PTP1B and hence another aspect of the invention comprises a computer-based method of rational drug design which comprises;

providing the structure of the PTP1B sulfenyl amide as defined by the coordinates of Table 1 or Table 2;

providing the structure of a candidate compound; and

fitting the structure of the candidate compound to the structure of the sulfenyl amide as defined by the coordinates of Table 1 or Table 2.

The invention further provides a method of identifying by rational drug design a compound capable of reducing the level of activity of a protein tyrosine phosphatase (PTP) in a cellular environment, the PTP being one which is convertible in a cellular environment between an active form and an inactive or less active form, the inactive form or less active form being characterised by the presence of a sulfenyl amide moiety formed at the active site of the PTP between

the sulphur atom of a cysteine group and a backbone nitrogen atom of a neighbouring amino acid;

which method comprises:

(a) designing a ligand that will (i) bind to the active site in the region of the sulfenyl amide moiety to inhibit conversion of the inactive form or less active form back to the active form, or (ii) modify the sulfenyl amide moiety to inhibit conversion of the inactive form or less active form of the PTP to the active form;

(b) synthesizing the ligand; and

(c) determining whether the ligand reduces the level of activity of a protein tyrosine phosphate (PTP) in a cellular environment.

In an alternative aspect, the method of the invention may utilise the coordinates of atoms of interest of the PTP1B which are in the vicinity of a putative binding region in order to model the pocket in which the a ligand will bind. These coordinates may be used to define a space which is then screened "*in silico*" against a candidate modulator molecule.

Thus the invention provides a computer-based method of rational drug design which comprises:

providing the coordinates of at least two atoms of Table 1 or Table 2 of the PTP1B sulfenyl amide ("selected coordinates");

providing the structure of a candidate modulator molecule; and

fitting the structure of candidate to the selected coordinates of the PTP1B sulfenyl amide.

In practice, it will be desirable to model a sufficient number of atoms of the PTP1B sulfenyl amide as defined by the coordinates of Table 1 or Table 2 which represent a binding pocket. Binding pockets and other features of the interaction of PTP1B sulfenyl amide with a putative compound of the invention are described below. Thus, in this embodiment of the invention, there will preferably be provided the coordinates of at least 5, preferably at least 10, more preferably at least 50 and even more preferably at least 100 atoms of the PTP sulfenyl amide structure.

By "fitting", it is meant determining by automatic, or semi-automatic means, interactions between at least one atom of the candidate and at least one atom of the PTP1B sulfenyl amide , and calculating the extent to which such an interaction is stable. Interactions include attraction and repulsion, brought about by charge, steric considerations and the like. Various computer-based methods for fitting are described further herein.

By "binding site" we mean a site (such as an atom, a functional group of an amino acid residue or a plurality of such atoms and/or groups) in a PTP1B sulfenyl amide binding cavity which may bind to a candidate ligand. Depending on the particular molecule in the cavity, sites may exhibit attractive or repulsive binding interactions, brought about by charge, steric considerations and the like.

As a result of the determination of the PTP1B sulfenyl amide 3D structure, more purely computational techniques for rational drug design may also be used to design PTP sulfenyl amide ligands (for an overview of these techniques see e.g Walters et al (*Drug Discovery Today*, Vol.3, No.4, (1998), 160-178; Abagyan, R.; Totrov, M. *Curr. Opin. Chem. Biol.* 2001, *5*, 375-382)). For example, automated ligand-receptor docking programs (discussed e.g. by Jones et al. in *Current Opinion in Biotechnology*, Vol.6, (1995), 652-656 and Halperin, I.; Ma, B.; Wolfson, H.; Nussinov, R. *Proteins* 2002, *47*, 409-443) which require accurate information on the atomic coordinates of target receptors may be used to design potential PTP1B sulfenyl amide ligands.

The step of providing the structure of a candidate ligand molecule may involve selecting the compound by computationally screening a database of compounds for interaction with the active site. For example, a 3-D descriptor for the candidate modulator may be derived, the descriptor including geometric and functional constraints derived from the architecture and chemical nature of the binding site. The descriptor may then be used to interrogate the compound database, a candidate ligand being a compound that has a good match to the features of the descriptor. In effect, the descriptor is a type of virtual pharmacophore.

In any event, the determination of the three-dimensional structure of PTP1B sulfenyl amide provides a basis for the design of new and specific ligands for PTP1B sulfenyl amide. For example, knowing the three-dimensional structure of PTP1B sulfenyl amides, computer modelling programs may be used to design different molecules expected to interact with possible or confirmed active sites, such as binding sites or other structural or functional features of PTP1B sulfenyl amide.

More specifically, a candidate ligand for PTP1B sulfenyl amide can be examined through the use of computer modelling using a docking program such as GOLD (Jones et al., *J. Mol. Biol.*, 245, 43-53 (1995), Jones et al., *J. Mol. Biol.,* 267, 727-748 (1997)), GRAMM (Vakser, I.A., *Proteins* , Suppl., 1:226-230 (1997)), DOCK (Kuntz et al, *J.Mol.Biol.* **1982** , *161*, 269-288, Makino et al, *J.Comput.Chem.* **1997**, *18*, 1812-1825), AUTODOCK (Goodsell et al, *Proteins* **1990**, *8*, 195-202, Morris et al, *J.Comput.Chem.* **1998**, *19*, 1639-1662.), FlexX, (Rarey et al, *J.Mol.Biol.* **1996**, *261*, 470-489) or ICM (Abagyan et al, *J.Comput.Chem.* **1994**, *15*, 488-506). . This procedure can include computer fitting of candidate ligands to PTP1B sulfenyl amide to ascertain how well the shape and the chemical structure of the candidate ligand will bind to the enzyme.

Also computer-assisted, manual examination of the active site structure of PTP1B may be performed. The use of programs such as GRID (Goodford, *J. Med. Chem.*, 28, (1985), 849-857) - a program that determines probable interaction sites between molecules with various functional groups and the enzyme surface - may also be used to analyse the active site to predict partial structures of ligands.

Computer programs can be employed to estimate the attraction, repulsion, and steric hindrance of the two binding partners (e.g. the PTP1B sulfenyl amide and a candidate ligand). Generally the tighter the fit, the fewer the steric hindrances, and the greater the attractive forces, the more potent the candidate ligand since these properties are consistent with a tighter binding constant. Furthermore, the more specificity in the design of a candidate ligand, the more likely it is that it will not

interact with other proteins as well. This will tend to minimise potential side-effects due to unwanted interactions with other proteins.

Linked fragment and fragment growing approaches.

If more than one PTP1B sulfenyl amide binding site is characterised and a plurality of respective compounds are designed or selected, the candidate ligand may be formed by linking the respective compounds into a larger compound which maintains the relative positions and orientations of the respective compounds at the active sites. The larger compound may be formed as a real molecule or by computer modelling.

Linked-fragment approaches to drug design also require accurate information on the atomic coordinates of target receptors. Small compounds which have the potential to bind to regions of PTP1B sulfenyl amide which in themselves may not be modulator compounds may be assembled by chemical linkage to provide candidate modulators. Thus the basic idea behind these approaches is to determine the binding locations of plural ligands to a target molecule, and then construct a molecular scaffold to connect the ligands together in such a way that their relative binding positions are preserved. The ligands may be provided computationally and modelled in a computer system, or provided in an experimental setting, wherein crystals according to the invention are provided and a plurality of ligands soaked separately or in mixed pools into the crystal prior to X-ray analysis and determination of their location.

For example, the binding of one or more molecular fragments can be determined in the protein binding cavity by X-ray crystallography. Molecular fragments are typically compounds with a molecular weight between 100 and 200 Da. This can then provide a starting point for medicinal chemistry to optimize the interactions using a structure-based approach. The fragments can be combined onto a template or used as the starting point for "growing out" a modulator into other cavities of the protein. The fragments can be positioned in the binding cavity or cavities of PTP1B sulfenyl amide and then 'grown' to fill the space available, exploring the electrostatic, van der Waals or hydrogen-bonding interactions that are involved in

molecular recognition. The potency of the original weakly binding fragment thus can be rapidly improved using iterative structure-based chemical synthesis.

At one or more stages in the fragment growing approach, the compound may be synthesized and tested in a biological system for its activity. This can be used to guide the further growing out of the fragment.

Where two fragment-binding regions are identified, a linked fragment approach may be based upon attempting to link the two fragments directly, or growing one or both fragments in the manner described above in order to obtain a larger, linked structure which may have the desired properties.

Thus the binding site of two of more ligands are determined and may be connected to thus form a potential lead compound that can be further refined using e.g. the iterative technique of Greer et al. For a virtual linked-fragment approach see Verlinde et al., *J. of Computer-Aided Molecular Design*, 6, (1992), 131-147, and for NMR and X-ray approaches see Shuker et al., *Science*, 274, (1996), 1531-1534 and Stout et al., *Structure*, 6, (1998), 839-848. The use of these approaches to design PTP1B sulfenyl amide modulators is made possible by the determination of the PTP1B sulfenyl amide structure.

Generation and Analysis of ligand-PTP1B sulfenyl amide complexes

In a further aspect, the invention provides a method for determining the structure of a compound bound to sulfenyl amide PTP1B. The methods above may comprise the further steps of:

obtaining or synthesising a candidate modulator;

forming a complex of PTP1B sulfenyl amide and said candidate modulator; and

analysing said complex by X-ray crystallography to determine the ability of said candidate modulator to interact with PTP1B sulfenyl amide.

The invention also provides a method for determining the structure of a compound bound to sulfenyl amide PTP1b, said method comprising: (a) providing a crystal of sulfenyl amide PTP1b according to the invention; (b) soaking the crystal with said

compound; and (c) determining the structure of said sulfenyl amide PTP1b compound complex by employing the data of Table 1 or Table 2.

Alternatively, the sulfenyl amide PTP1B and compound may be co-crystallized. Thus the invention provides a method for determining the structure of a compound bound to sulfenyl amide PTP1b, said method comprising; mixing the protein with the compound(s), crystallizing the protein-compound(s) complex; and determining the structure of said sulfenyl amide PTP1b -compound(s) complex by reference to the data of Table 1 or Table 2.

A mixture of compounds may be soaked or co-crystallized with the crystal, wherein only one or some of the compounds may be expected to bind to the sulfenyl amide PTP1b. As well as the structure of the complex, the identity of the complexing compound(s) is/are then determined.

In either case, substrate or a substrate analogue thereof may optionally be present.

The method may comprise the further steps of: (a) obtaining or synthesising said compound; (b) forming a complex of sulfenyl amide PTP1B and said compound; and (c) analysing said complex by X-ray crystallography or NMR spectroscopy to determine the ability of said compound to interact with sulfenyl amide PTP1b.

This information may thus be used to design and synthesize novel classes of sulfenyl amide PTP1B inhibitors.

Detailed structural information can then be obtained about the binding of the candidate modulator to PTP1B sulfenyl amide, and in the light of this information adjustments can be made to the structure or functionality of the candidate modulator, e.g. to improve binding to the active site. The above steps may be repeated and re-repeated as necessary.

In another aspect, the invention provides a method of analysing a complex of PTP1B sulfenyl amide and a candidate modulator comprising the step of employing (i) X-ray crystallographic diffraction data from the complex and (ii) a three-

dimensional structure of PTP1B sulfenyl amide, or at least one sub-domain thereof, to generate a difference Fourier electron density map of the complex, the three-dimensional structure being defined by atomic coordinate data according to Table 1 or Table 2.

Therefore, such complexes can be crystallised and analysed using X-ray diffraction methods, e.g. according to the approach described by Greer et al., *J. of Medicinal Chemistry*, Vol. 37, (1994), 1035-1054, and difference Fourier electron density maps can be calculated based on X-ray diffraction patterns of soaked or co-crystallised PTP1B sulfenyl amide and the solved structure of uncomplexed PTP1B sulfenyl amide. These maps can then be used to determine whether and where a particular candidate modulator binds to PTP1B sulfenyl amide and/or changes the conformation of PTP1B sulfenyl amide.

Electron density maps can be calculated using programs such as those from the CCP4 computing package (Collaborative Computational Project 4. The CCP4 Suite: Programs for Protein Crystallography, *Acta Crystallographica*, D50, (1994), 760-763.). For map visualisation and model building programs such as "O" (Jones et al., *Acta Crystallograhy*, A47, (1991), 110-119) or QUANTA" (1994, San Diego, CA: Molecular Simulations, Jones et al., Acta Crystallography A47 (1991), 110-119) can be used.

Greer et al. mentioned above describes an iterative approach to ligand design based on repeated sequences of computer modelling, protein-ligand complex formation and X-ray analysis. Thus novel thymidylate synthase inhibitor series were designed *de novo* by Greer et al., and PTP1B sulfenyl amide inhibitors may also be designed in the this way. More specifically, using e.g. GRID on the solved 3D structure of PTP1B, a candidate modulator for PTP1B sulfenyl amide may be designed that complements the functionalities of the PTP1B sulfenyl amide binding site(s). The candidate modulator compound can then be synthesised, formed into a complex with PTP1B sulfenyl amide, and the complex then analysed by X-ray crystallography to identify the actual position of the bound compound.

Determination of the position of the candidate modulator in the complex allows determination of the interactions of it with PTP1B sulfenyl amide. This will allow those of skill in the art to analyse the affinity and specificity of the compound for PTP1B sulfenyl amide, and to propose modifications to the compound to increase or decrease either or both of these properties. Thus the structure and/or functional groups of the compound can then be adjusted, if necessary, in view of the results of the X-ray analysis, and the synthesis and analysis sequence repeated until an optimised compound is obtained. Related approaches to structure-based drug design are also discussed in Bohacek et al., *Medicinal Research Reviews*, Vol.16, (1996), 3-50.

Many of the techniques and approaches to structure-based drug design described above require X-ray analysis to identify the binding position of a candidate modulator in a complex with a protein. A common way of doing this is to perform X-ray crystallography on the complex, produce a difference Fourier electron density map, and associate a particular pattern of electron density with the candidate modulator. However, in order to produce the map (as explained e.g. by Blundell et al. mentioned above) it is necessary to know beforehand the protein 3D structure (or at least the protein structure factors).

Therefore, determination of the PTP1B sulfenyl amide structure also allows difference Fourier electron density maps of complexes of PTP1B sulfenyl amide with a candidate modulator to be produced, which can greatly assist the process of rational drug design.

The approaches to structure-based drug design described above all require initial identification of possible compounds for interaction with target bio-molecule (in this case PTP1B sulfenyl amide). Sometimes these compounds are known e.g. from the research literature. However, when they are not, or when novel compounds are wanted, a first stage of the drug design program may involve computer-based *in silico* screening of compound databases (such as the Cambridge Structural Database) with the aim of identifying compounds which interact with the binding site or sites of the target bio-molecule (see Martin, *J. Med. Chem.*, vol 35,

2145-2154 (1992)). Screening selection criteria may be based on pharmacokinetic properties such as metabolic stability and toxicity. However, determination of the PTP1B sulfenyl amide structure allows the architecture and chemical nature of each PTP1B active site to be identified, which in turn allows the geometric and functional constraints of a descriptor for the potential inhibitor to be derived. The descriptor is, therefore, a type of virtual 3-D pharmacophore, which can also be used as selection criteria or filter for database screening.

The Crystal Structure of the Catalytic Domain of PTP1B Sulfenyl Amide

The structure of the portion of the PTP sulfenyl amide corresponding to the catalytic domain of PTP1B is defined by the atomic coordinates set out in Table 1 or Table 2. The three dimensional structure of the binding sites of the PTP1B sulfenyl amide are shown schematically in Figures 1b and 1c.

The crystal structure shows electron density close to the side chain of the catalytic cysteine characteristic of the presence of a covalent bond between the sulphur Sγ atom of Cys215 and the backbone nitrogen atom of Ser216 (see Figure 1c). The sulfenyl-amide bond has a bond length of 1.7 Å and results in a five-membered puckered ring that has not been previously observed in proteins. In conjunction with the formation of the sulfenyl-amide derivative the phosphate-binding cradle adopts a novel conformation, distinct from the structure of the known inactive C215S PTP1B mutant[16]. The cradle has shifted into the phosphotyrosine binding site and stabilises the sulfenyl-amide by a hydrophobic interaction with the side chain of Ile219 (Figure 1b). In addition, the side chain of Gln262 moves out of the active site and also the pTyr loop adopts a unique conformation (Figure 1b). The more exposed conformation of the pTyr loop results from the loss of the hydrogen bond between the hydroxyl groups of Tyr46 and Ser216, which anchors the pTyr loop in native PTP1B and is stabilised by a network of water molecules mediating interactions between Asp48 and the rest of the protein.

Formation of the sulfenyl-amide arises from oxidation of the active site Cys215, most likely via oxidation of Cys215 to sulfenic acid, followed by a nucleophilic attack of the backbone nitrogen atom of Ser216 on the Sγ atom of Cys215. Indeed,

it has been postulated that the hydrogen bond interaction between the carbonyl oxygen atom of Cys215 and the N1 atom of the invariant His214 side chain in native PTP1B increases the partial charge on the backbone nitrogen atom of Ser216[12], enhancing its reactivity and supporting a nucleophilic substitution mechanism. *In vivo* the sulfenic acid can be formed by oxidation with hydrogen peroxide (H_2O_2)[17], but under our experimental conditions it is most likely triggered by redox-cycling of 2-Phenyl-isoxazolidine-3,5-dione (figure 2). The leaving group in the cyclisation reaction could be a water molecule in an SN_2 substitution reaction (direct mechanism, Figure 2). Alternatively, the sulfenic acid derivative might be oxidised under the experimental soaking conditions, or by physiological oxidants such as hydrogen peroxide or oxidised glutathione *in vivo*, to form a highly reactive intermediate. This would result in faster formation of the sulfenyl-amide species (oxidative mechanism, Figure 2).

The role for the sulfenyl-amide intermediate in oxidative regulation of PTP1B in cells is likely to be the prevention of irreversible oxidation of Cys215 and thus facilitation of its thiol-mediated reactivation (Figure 2). To demonstrate the reversibility of the S-N bond, reducing conditions were employed in an attempt to reduce the sulfenyl-amide derivative in the crystals. First, two PTP1B crystals were soaked in a solution containing 2-Phenyl-isoxazolidine-3,5-dione. X-ray data collected from one of the crystals confirmed the formation of the sulfenyl-amide bond and the concomitant conformational changes in the active site. The second crystal was back-soaked in 20mM reduced glutathione in an attempt to reduce the Cys215 sulfenyl-amide derivative back to its native form. Indeed, X-ray data collected from the back-soaked crystal showed the entire active site back in its native conformation, thus structurally confirming reactivation of the sulfenyl-amide PTP1B derivative by a biologically relevant reducing agent and strengthening the hypothesis of a protective role in PTP1B redox-regulation.

The studies carried out provide a detailed structural understanding of the intermediates involved in redox-regulation of PTP1B and reveal a novel oxidation state of its catalytic cysteine. The formation of the sulfenyl-amide intermediate is an elegant mechanism to protect Cys215 from further oxidation, and the

concomitant conformational changes of the phosphate-binding cradle and pTyr loop may serve to signal the inactive state of the enzyme. The structures of the sulfenic acid and sulfenyl-amide derivative indicate that reactivation of PTP1B appears to be facilitated by the sulfenyl-amide form.

The sulfenyl-amide form of PTPs is an important regulatory intermediate of these proteins. It is stable to oxidation to the sulfinic or sulfonic protein forms that are irreversibly inhibited and therefore prevents permanent inactivation of the protein. It can then subsequently be converted to the reduced, active form of the protein by physiological reducing agents such as thiols. The sulfenyl amide is an isothiazolidin-3-one ring system, which has not been previously observed in proteins. It is an electrophilic species in the active site of an enzyme, and this is also very unusual as most enzymes display nucleophiles in their catalytic machinery.

Therapeutic and Medical Uses of the Inhibitors of PTP Sulfenyl Amide

It is envisaged that compounds that stabilize the sulfenyl amide form or effect reversible or irreversible covalent modification of the sulfenyl amide form will be useful as therapeutic agents in the treatment of disease states or conditions mediated by protein tyrosine phosphatases.

Accordingly, in one aspect, the invention provides the use of a compound for the manufacture of a medicament for the treatment of a disease or condition mediated by protein tyrosine phosphatase, wherein the compound is one that binds to protein tyrosine phosphatase sulfenyl amide to prevent or inhibit conversion of the protein tyrosine phosphatase sulfenyl amide to an active reduced form of the protein tyrosine phosphatase.

In a further aspect, the invention provides a method of reducing the activity of a protein tyrosine phosphotase (PTP), the PTP being one which is convertible between an active form and an inactive or less active form, the inactive or less active form being characterised by the presence of a sulfenyl amide moiety formed at the active site of the PTP between the sulphur atom of a cysteine group and a backbone nitrogen atom of a neighbouring amino acid, whereby the sulfenyl amide

moiety distorts and inactivates the active site of the PTP and wherein the sulfenyl amide moiety is disruptible to restore the inactive or less active form of the PTP to the active form thereof;

which method comprises inhibiting disruption of the sulfenyl amide moiety, or modifying the sulfenyl amide moiety to prevent restoration of the inactive or less active form of the PTP to the active form.

In another aspect, the invention provides a method of inhibiting or preventing the reduction of sulfenyl amide PTP1B to PTP1B in a cellular environment by exposing the PTP1B to a ligand capable of binding to the sulfenyl amide PTP1B in the region of the sulfenyl amide moiety so as to prevent reduction of the sulfenyl amide moiety by an intracellular reducing agent.

The invention also provides a method of inhibiting or preventing the reduction of sulfenyl amide PTP1B to PTP1B in a cellular environment by exposing the PTP1B to a ligand capable of binding to the sulfenyl amide PTP1B in the region of the sulfenyl amide moiety, the ligand having a nucleophilic moiety capable of modifying the sulfenyl amide moiety so as to prevent its reduction by an intracellular reducing agent.

The Compounds of the Invention

The invention provides novel compounds *per se* that inhibit protein tyrosine phosphatases by interacting with the sulfenyl amide PTP to prevent or inhibit conversion of the PTP sulfenyl amide to an active reduced form of the protein tyrosine phosphatase.

In addition to compounds *per se*, the invention provides compounds of the aforesaid type for use in therapy or for use in medicine, for example for use in the treatment of diseases or conditions mediated by protein tyrosine phosphatase.

Conversion of the PTP sulfenyl amide to the corresponding active reduced form can be inhibited in several ways by small molecule ligands.

Mode 1. Non-covalent binding inhibitors that stabilise the sulfenyl-amide protein form. These inhibitors are designed to prevent physiological cell cycling of the protein form into its active reduced form by preventing binding to the protein.

Mode 2. Reversible covalent binding inhibitors that modify the sulfenyl-amide form of the protein. These inhibitors are designed to react with the active site sulfenyl amide, and in so doing, prevent its reactivation by physiological cell cycling.

Mode 3. Irreversible covalent binding inhibitors that modify the sulfenyl-amide form of the protein. These inhibitors are designed to react with the active site sulfenyl amide, and in so doing, prevent its reactivation by physiological cell cycling.

The concerted distortion of the phosphate binding cradle and phosphotyrosine recognition loop upon sulfenyl-amide formation destroys the normal phosphotyrosine binding site and creates a new groove (referred to herein as "the first binding site") in which small molecules could bind. This groove is lined by residues 41-47 of the phosphotyrosine recognition loop, residues 88-90, 115 to 120, residues 179 to 184 of the WPD-loop, residues 215 to 219 of the phosphate-binding cradle, and residues 262-266.

Compounds having *Mode 1* activity include compounds that can make polar interactions at the first binding site with one or more of:

(1) Lys41
(2) Asn42
(3) Arg45
(4) Tyr46
(5) Arg47
(6) Asn90
(7) Gln115
(8) Lys116
(9) Ser118
(10) Lys120
(11) Trp179

(12) Ser 216
(13) Arg221
(14) Gln262
(15) Thr263
(16) Asp265, and
(17) Gln266

The amino acid numbering convention used above refers to the numbering of PTP1B.

Preferably, the compounds make polar interactions with two or more of the listed moieties (1) to (17), more preferably three or more, for example four or more, and more particularly five or more.

The compounds can make hydrophobic interactions with one or more of:

(18) Leu88
(19) Pro89
(20) Leu119
(21) Phe182
(22) Gly183
(23) Val184
(24) Ala217
(25) Ile219
(26) the apolar part of Arg221, and
(27) the apolar part of Gln262.

Preferably, the compounds make hydrophobic interactions with two or more of the listed moieties, more preferably three or more, for example five or more.

Additional hydrogen bonds and hydrophobic interactions may be formed between a bound molecule and the protein backbone.

A second shallow depression in which a small molecule could bind (referred to hereinafter as "the second binding site") is located on the other side of the distorted protein tyrosine recognition loop and includes residues from the second phosphate

binding site in PTP1B. This potential binding area is roughly defined by residues of the WPD-loop, the pTyr recognition loop and the loop containing residues 28-32.

Compounds having *Mode 1* activity include compounds that can make polar interactions at the second binding site with one or more of:

(44) Arg24
(14) Gln262
(45) Arg254
(46) Asn 44
(5) Arg47
(4) Tyr46
(1) Lys 41
(47) Lys36
(48) Asp29
(49) Cys32
(50) Ser50

The compounds can make hydrophobic interactions with one or more of:

(51) Leu250
(14) Gln262
(41) Met258
(35) Val49
(4) Tyr46
(39) Gly218
(52) Gly259
(53) Phe52
(42) Leu260
(54) Leu261
(55) Ala35 and
(56) the backbone of Asp48.

In the middle of this binding area a third potential binding site (hereinafter referred to as "the third binding site") has been created as a result of the distortion of the

phosphate-binding cradle. This water filled cavity is located directly under the distorted phosphate-binding cradle and has a narrow entrance between residues Val49, Gly218 and Gln 262. The cavity walls are formed by Asp48, Val49, Leu83, Gly218, Gly220, Ser222, Arg257, Gly259, Gln262 and the sulfenyl-amide.

Accordingly, compounds having *Mode 1* activity include compounds that can make polar interactions at the third binding site with one or more of:

(3) Arg45

(29) Asp48

(30) Ser222

(31) Arg257

(14) Gln262

(33) the protein backbone of one or more of (i) Thr84, (ii) Gly218, (iii) Gly220, (iv) Gly223, (v) Met258, (vi) and Gly259;

(34) and the sulfenyl-amide residue.

Preferably the compounds can make polar interactions at two or more (more preferably three or more, four or more, or five or more) of the residues (3), (29) to (31), (14), (33) and (34).

Hydrophobic interactions with the compound can be made at the third binding site by:

(35) Val49

(36) Leu83

(37) Gln85

(38) Gly86

(39) Gly218

(40) Gly220

(41) Met258

(42) Leu260 and

(43) the main chain of His214.

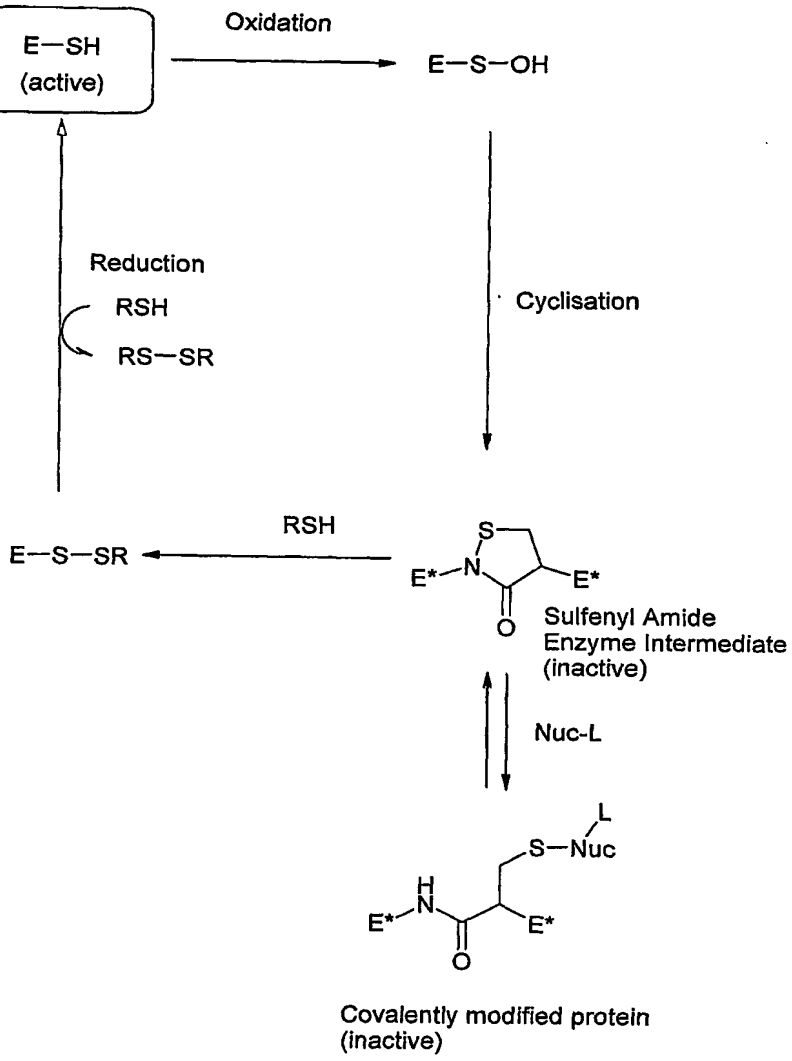
Preferred interactions between the compounds of the invention and the three binding sites described above are as follows:

First binding site:
Polar: Trp79, Arg221, Lys46, Glu266, Arg45, Ser118
Hydrophobic: Ile219, Leu88, Ile120

Second binding site:
Polar: Arg254, Lys36, Asp29, Gln262
Hydrophobic: Met258, Val49

Third binding site (cavity):
Polar: Arg257, Asp48, Ser222
Hydrophobic: sulfenyl amide, Val 49, Leu83

As described above, compounds useful in the invention include those that bind to the sulfenyl amide PTP in the region of the sulfenyl amide moiety thereby to prevent reduction or other reaction of the sulfenyl amide with an endogenous intracellular molecule such as glutathione and conversion back to the active form of the PTP. However, in an alternative embodiment of the invention, the compounds can be ligands that possess a nucleophilic functional group that can react either reversibly (*Mode 2*) or irreversibly (*Mode 3*) with the electrophilic sulfenyl amide active. Scheme 1 below illustrates how ligands inhibit the action of the protein in the cell by preventing it from being converted back to an active form.



SCHEME 1

The compounds of the invention can thus take the form of nucleophilic ligands, having a nucleophilic group that will react with the sulfenyl amide moiety, and a binding region for binding to the sulfenyl amide PTP in the region of the sulfenyl amide moiety. The binding region can be one that exhibits one or more of the polar and non-polar interactions 1 to 56 set out above in relation to *Mode 1* compounds.

The nucleophilic group will typically contain a heteroatom (e.g. selected from nitrogen, sulphur, oxygen and phosphorus) that is either neutral or negatively

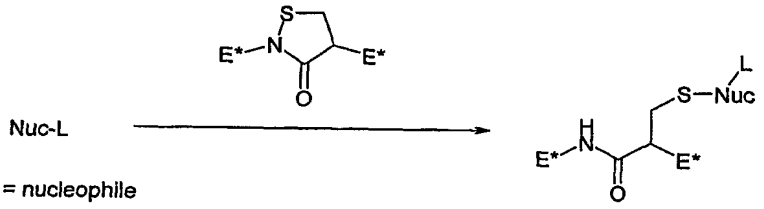
charged, and which may be located adjacent a carbon atom or another heteroatom, which is capable of reacting with the sulfenyl amide species. Nitrogen, oxygen and sulfur nucleophiles are preferred.

Thus, the sulfenyl amide moiety can be modified by reaction with a nucleophilic ligand to prevent it from reverting to the active form of the enzyme.

The nucleophilic group is selected from the group consisting of a thiol, disulfane, primary thioamide, secondary thioamide, primary thiourea, secondary thiourea, primary amine, secondary amine, primary hydrazine, secondary hydrazine, primary hydrazide, secondary hydrazide, primary hydrazone, secondary hydrazone, primary amide, secondary amide, primary urea, secondary urea, primary sulfonamide, secondary sulfonamide, 5-membered ring heterocycle containing NH, alcohol, hydroxylamine, oxime, hydroxamic acid, carboxylic acid (preferably other than an oxalamic acid), sulfoxide, sulfate and a nitrone.

Particular examples of nucleophiles are set out in Table 3 below.

Table of Nucleophiles

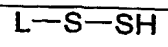
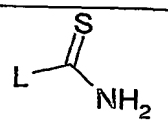
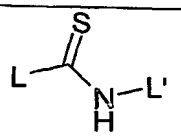
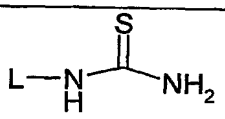
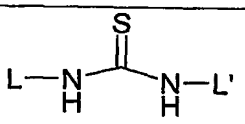
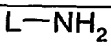
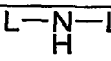
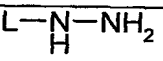
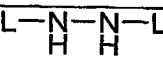
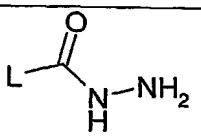
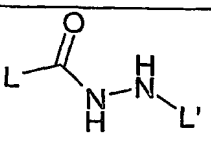


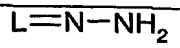
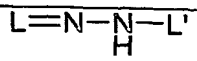
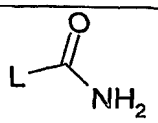
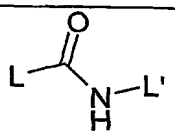
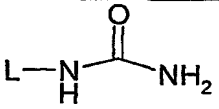
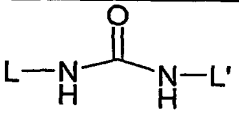
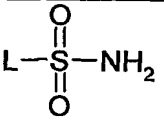
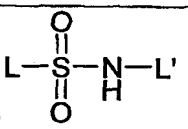
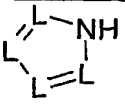
Nuc = nucleophile

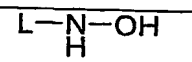
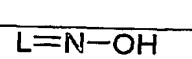
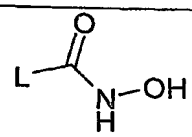
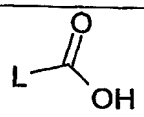
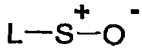
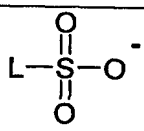
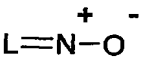
L = Ligand

Table 3

Type of nucleophile	Structure	Name
Sulphur	L—SH	Thiol

		Disulfane
		Primary Thioamide
		Secondary Thioamide
		Primary thiourea
		Secondary thiourea
Nitrogen		Primary amine
		Secondary amine
		Primary Hydrazine
		Secondary Hydrazine
		Primary Hydrazide
		Secondary Hydrazide

		Primary Hydrazone
		Secondary Hydrazone
		Primary amide
		Secondary amide
		Primary urea
		Secondary urea
		Primary Sulfonamide
		Secondary Sulfonamide
		5-membered ring heterocycle containing NH
Oxygen		Alcohol

		Hydroxylamine
		Oxime
		Hydroxamic acid
		Carboxylic acid (preferably not oxalamic acids)
		Sulfoxide
		Sulfate
		Nitrone

In the table, the symbols L and L' represents the residue of the ligand, other than the nucleophilic group. The residue may of course contain one or more further nucleophilic groups of the type shown.

Compounds of the invention that are nucleophilic ligands will form new covalently bound protein-ligand species. In some cases (*Mode 2*), the protein-ligand species is capable of undergoing the reverse reaction to reform the sulfenyl amide. In other cases (*Mode* 3), the nucleophiles will form a covalently bound protein-ligand complex in which the reverse reaction does not occur in the environment of the active site, or occurs very slowly, so that the complex is formed irreversibly. Additionally, certain covalent protein-ligand complexes, formed by reaction of

nucleophilic ligands with the sulfenyl amide protein, may undergo additional reactions that prevent the reverse reaction from occurring, resulting in irreversible inhibition.

For example, where the nucleophilic heteroatom is an oxygen atom, the resulting covalent protein-ligand complex will contain a sulfur oxygen bond which is therefore oxidised. Subsequent further oxidation under cellular conditions could lead to oxidation of the protein to sulfinyl or sulfonic acid oxidation states, irreversibly modifying the protein.

The compounds of the invention are typically synthetic compounds that are not normally encountered in a cellular environment, although naturally occurring compounds derived from plant sources, marine sources or other non-mammalian sources may be used where appropriate.

The compounds of the invention are typically organic compounds and can be non-peptides, peptides or modified peptides. In one embodiment, the compounds are not peptides.

The compounds of the invention may comprise a scaffold formed from one or more optionally substituted carbocyclic or heterocyclic ring systems, the ring systems and/or the substituents having one or more polar or non-polar moieties for interacting with one or more, preferably a plurality of the binding sites 1 to 43 listed above.

The carbocyclic and heterocyclic ring systems can be aromatic or non-aromatic ring systems. When the carbocyclic or heterocyclic groups are aryl or heteroaryl groups, they can have, for example, from 5 to 12 ring members, more usually from 5 to 10 ring members. The term "aryl" as used herein refers to a carbocyclic group having aromatic character and the term "heteroaryl" is used herein to denote a heterocyclic group having aromatic character. The terms "aryl" and "heteroaryl" embrace polycyclic (e.g. bicyclic) ring systems wherein one or more rings are non-aromatic, provided that at least one ring is aromatic. The aryl or heteroaryl groups can be monocyclic or bicyclic groups and can be unsubstituted or substituted with one or

more substituents. Examples of heteroaryl groups are monocyclic and bicyclic groups containing from five to twelve ring members, and more usually from five to ten ring members. The heteroaryl group can be, for example, a five membered or six membered monocyclic ring or a bicyclic structure formed from fused five and six membered rings or two fused six membered rings. Each ring may contain up to about four heteroatoms typically selected from nitrogen, sulphur and oxygen. Typically the heteroaryl ring will contain up to 3 heteroatoms, more usually up to 2, for example a single heteroatom. In one embodiment, the heteroaryl ring contains at least one ring nitrogen atom. The nitrogen atoms in the heteroaryl rings can be basic, as in the case of imidazole or pyridine, or essentially non-basic as in the case of an indole or pyrrole nitrogen. In general the number of basic nitrogen atoms present in the heteroaryl group, including any amino group substituents of the ring, will be less than five.

Examples of heteroaryl groups include but are not limited to pyridyl, pyrrolyl, furanyl, thiophenyl, imidazolyl, oxazolyl, oxadiazolyl, oxatriazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, pyrazinyl, pyrimidinyl, triazinyl, triazolyl, tetrazolyl, quinolinyl, isoquinolinyl, benzfuranyl, benzthiophenyl, chromanyl, thiochromanyl, benzimidazolyl, benzoxazolyl, benzisoxazole, benzthiazolyl and benzisothiazole, isobenzofuranyl, isoindolyl, indolizinyl, indolinyl, isoindolinyl, purinyl (e.g., adenine, guanine), indazolyl, benzodioxolyl, chromenyl, isochromenyl, chroman, isochromanyl, benzodioxanyl, quinolizinyl, benzoxazinyl, benzodiazinyl, pyridopyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, phthalazinyl, naphthyridinyl and pteridinyl.

Examples of carbocyclic aryl groups include phenyl, naphthyl, indenyl, and tetrahydronaphthyl.

Examples of non-aromatic heterocyclic groups are groups having from 3 to 12 ring members, more usually 5 to 10 ring members. Such groups can be monocyclic or bicyclic, for example, and typically have from 1 to 5 heteroatom ring members (more usually 1, 2, 3 or 4 heteroatom ring members), usually selected from

nitrogen, oxygen and sulphur. The heterocylic groups can contain, for example, cyclic ether moieties (e.g as in tetrahydrofuran and dioxane), cyclic thioether moieties (e.g. as in tetrahydrothiophene), cyclic amine moieties (e.g. as in pyrrolidine), cyclic sulphones (e.g. as in sulfolane and sulfolene)), cyclic sulphoxides, cyclic sulphonamides and combinations thereof.

Particular examples include morpholine, piperidine, pyrrolidine, pyrrolidone, tetrahydrofuran, tetrahydrothiophene, dioxan, tetrahydropyran, imidazoline, imidazolidinone, oxazoline, thiazoline, piperazine, and N-alkyl piperazines such as N-methyl piperazine. In general, preferred non-aromatic heterocyclic groups include tetrahydrofuran, morpholine, piperazine, piperidine, pyrrolidine and pyrrolidone.

The carbocyclic and heterocyclic groups can each be unsubstituted or substituted by one or more substituent groups selected from halogen, hydroxy, trifluoromethyl, cyano, nitro, carboxy, amino, carbocyclic and heterocyclic groups having from 3 to 12 ring members; a group R^a-R^b wherein R^a is a bond, O, CO, $X^1C(X^2)$, $C(X^2)X^1$, $X^1C(X^2)X^1$, S, SO, SO_2, NR^cR^d, SO_2NR^c or NR^cSO_2; and R^b is selected from hydrogen, carbocyclic and heterocyclic groups having from 3 to 7 ring members, and a C_{1-8} hydrocarbyl group optionally substituted by one or more substituents selected from hydroxy, oxo, halogen, cyano, nitro, amino, mono- or di-C_{1-4} hydrocarbylamino, carbocyclic and heterocyclic groups having from 3 to 12 ring members and wherein one or more carbon atoms of the C_{1-8} hydrocarbyl group may optionally be replaced by O, S, SO, SO_2, NR^c, $X^1C(X^2)$, $C(X^2)X^1$ or $X^1C(X^2)X^1$;

R^c and R^d are the same or different and each is hydrogen or C_{1-4} hydrocarbyl;

X^1 is O, S or NR^c and X^2 is =O, =S or $=NR^c$.

Where the substituent group comprises or includes a carbocyclic or heterocyclic group, the said carbocyclic or heterocyclic group may be unsubstituted or may itself be substituted with one or more further substituent groups. In one sub-group of compounds of the formula (I), such further substituent groups may include carbocyclic or heterocyclic groups, which are typically not themselves further

substituted. In another sub-group of compounds of the formula (I), the said further substituents do not include carbocyclic or heterocyclic groups but are otherwise selected from the groups listed above in the definition of the substituents.

Examples of halogen substituents include fluorine, chlorine, bromine and iodine. Fluorine and chlorine are particularly preferred.

In the definition of the compounds above and as used hereinafter, the term "hydrocarbyl" is a generic term encompassing aliphatic, alicyclic and aromatic groups having an all-carbon backbone, except where otherwise stated. Examples of such groups include alkyl, cycloalkyl, cycloalkenyl, carbocyclic aryl, alkenyl, alkynyl, cycloalkylalkyl, cycloalkenylalkyl, and carbocyclic aralkyl, aralkenyl and aralkynyl groups. Such groups can be unsubstituted or substituted by one or more substituents as defined herein. The examples and preferences expressed below apply to each of the hydrocarbyl substituent groups or hydrocarbyl-containing substituent groups referred to in the various definitions of substituents for compounds of the invention unless the context indicates otherwise.

The term "alkyl" covers both straight chain and branched chain alkyl groups. Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, 2-pentyl, 3-pentyl, 2-methyl butyl, 3-methyl butyl, and n-hexyl and its isomers.

Examples of cycloalkyl groups are those derived from cyclopropane, cyclobutane, cyclopentane, cyclohexane and cycloheptane.

Examples of alkenyl groups include, but are not limited to, ethenyl (vinyl), 1-propenyl, 2-propenyl (allyl), isopropenyl, butenyl, buta-1,4-dienyl, pentenyl, and hexenyl.

Examples of cycloalkenyl groups include, but are not limited to, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclopentadienyl and cyclohexenyl.

Examples of alkynyl groups include, but are not limited to, ethynyl and 2-propynyl (propargyl) groups.

Examples of carbocyclic aryl groups include substituted and unsubstituted phenyl.

Examples of cycloalkylalkyl, cycloalkenylalkyl, carbocyclic aralkyl, aralkenyl and aralkynyl groups include phenethyl, benzyl, styryl, phenylethynyl, cyclohexylmethyl, cyclopentylmethyl, cyclobutylmethyl, cyclopropylmethyl and cyclopentenylmethyl groups.

The definition "R^a-R^b" as used herein, includes *inter alia* compounds wherein R^a is selected from a bond, O, CO, OC(O), SC(O), $NR^cC(O)$, OC(S), SC(S), $NR^cC(S)$, $OC(NR^c)$, $SC(NR^c)$, $NR^cC(NR^c)$, C(O)O, C(O)S, $C(O)NR^c$, C(S)O, C(S)S, $C(S)NR^c$, $C(NR^c)O$, $C(NR^c)S$, $C(NR^c)NR^c$, OC(O)O, SC(O)O, $NR^cC(O)O$, OC(S)O, SC(S)O, $NR^cC(S)O$, $OC(NR^c)O$, $SC(NR^c)O$, $NR^cC(NR^c)O$, OC(O)S, SC(O)S, $NR^cC(O)S$, OC(S)S, SC(S)S, $NR^cC(S)S$, $OC(NR^c)S$, $SC(NR^c)S$, $NR^cC(NR^c)S$, $OC(O)NR^c$, $SC(O)NR^c$, $NR^cC(O)NR^c$, $OC(S)NR^c$, $SC(S)NR^c$, $NR^cC(S)NR^c$, $OC(NR^c)NR^c$, $SC(NR^c)NR^c$, $NR^cC(NR^cNR^c$, S, SO, SO_2, NR^cR^d, SO_2NR^c and NR^cSO_2 wherein R^c is as hereinbefore defined.

The moiety R^b can be hydrogen or it can be a group selected from carbocyclic and heterocyclic groups having from 3 to 12 ring members (typically 3 to 10 and more usually from 5 to 10), and a C_{1-8} hydrocarbyl group optionally substituted as hereinbefore defined.

Examples of hydrocarbyl, carbocyclic and heterocyclic groups are as set out above.

When present, the hydrocarbyl group can be substituted by one or more substituents selected from hydroxy, oxo, halogen, cyano, nitro, amino, mono- or di-C_{1-4} hydrocarbylamino, and monocyclic carbocyclic and heterocyclic groups having from 3 to 12 (typically 3 to 10 and more usually 5 to 10) ring members. Preferred

substituents include halogen such as fluorine. Thus, for example, the substituent can be a partially fluorinated or perfluorinated group such as trifluoromethyl.

One or more carbon atoms of the C_{1-8} hydrocarbyl group may optionally be replaced by O, S, SO, SO_2, NR^c, $X^1C(X^2)$, $C(X^2)X^1$ or $X^1C(X^2)X^1$ wherein X^1 and X^2 are as hereinbefore defined. For example, 1, 2, 3 or 4 carbon atoms of the hydrocarbyl group may be replaced by one of the atoms or groups listed, and the replacing atoms or groups may be the same or different. Examples of groups in which a carbon atom of the hydrocarbyl group has been replaced by a replacement atom or group as defined above include ethers and thioethers (C replaced by O or S), amides, esters, thioamides and thioesters (C replaced by $X^1C(X^2)$ or $C(X^2)X^1$), sulphones and sulphoxides (C replaced by SO or SO_2) and amines (C replaced by NR^c).

The combination of ring system and substituents is chosen so as to give a desired level of interaction with residues (1) to (56) in the three binding sites defined above. The extent of the interaction between the compound and the binding sites of the PTP sulfenyl amide can be gauged using the computer based modelling methods discussed above based on the atomic coordinates set out in Table 1 or Table 2.

In general, the number of interactions between the compound and the PTP sulfenyl amide may be chosen so as to optimise the binding of the compound to the PTP sulfenyl amide. For *Mode 1* inhibitor compounds, in one embodiment, it is preferred to maximise the number of interactions between the compound and the first and/or second and/or third binding sites so as to provide enhanced binding to the PTP sulfenyl amide.

For example, where the compound is designed to bind to the first binding site, it is preferred that the compound makes polar interactions with at least seven, more usually at least ten, and preferably at least twelve of the residues (1) to (17) and hydrophobic interactions with at least two and more preferably at least four of the residues (18) to (27).

Where the compound is designed to bind to the second binding site, it is preferred that the compound forms polar interactions with at least two, more usually three, and preferably four of the residues (44), (14), (45), (46), (5), (4), (1), (47), (48), (49) and (50), and hydrophobic interactions with at least one or two of the residues (51), (14), (41), (35), (4), (39), (52), (53), (42), (54), (55) and (56).

Where the compound is designed to bind to the third binding site, it is preferred that the compound forms polar interactions with at least two, more usually three, and preferably at least four of the residues (3), (29), (30), (31), (14), (33) and (34), and preferably at least two and more usually at least three hydrophobic interactions with the residues (35), (36), 37), (38), (39), (40), (41), (42) and (43).

In one embodiment of the invention, the compound forms interactions at two or more of the first, second and third binding sites, for example, (i) the first and second binding sites, or (ii) the first and third, or (iii) the second and third binding sites.

In another embodiment, the compound forms interactions with only the first binding site.

In a further embodiment, the compound forms interactions with only the second binding site.

In a further embodiment, the compound forms interactions with only the third binding site.

In a still further embodiment, the compound forms interactions with all three binding sites.

A compound is considered to have formed an interaction with a given residue at a binding site if the proximity between a compound or portions thereof to the molecule or portions thereof wherein the juxtaposition is energetically favored by electrostatic or van der Waals interactions. The distance will depend on the type of interaction made-hydrogen bond, salt bridge or stacking interaction

The term hydrogen bond refers to a favorable interaction that occurs whenever a suitable donor atom, Q^X, bearing a proton, H, and a suitable acceptor atom, Q^Y, have a separation of < 3.5Å and where the angle Q^X-H-Q^Y is greater than 90 degrees. Sometimes, a single proton on a donor atom Q^X may form a plurality of suitable acceptor atoms, Q^Y. For example, the proton on a -NH-group may form a separate hydrogen bond with each of the two oxygen atoms in a carboxylate anion. Suitable donor and acceptor atoms are well understood in medicinal chemistry (G.C. Pimentel and A.L. McClellan, The Hydrogen Bond, Freeman, San Francisco, 1960; R. Taylor and 0. Kennard, Hydrogen Bond Geometry in organic Crystals, Accounts of Chemical Research, 17, pp. 320-326 (1984)).

The term "hydrogen bonding moiety" refers to a chemical structure containing one or more suitable hydrogen bond donor moieties or hydrogen bond acceptor moieties.

The term "hydrogen bonding donor moiety" refers to a chemical structure containing a suitable hydrogen bond donor atom bearing one or more protons. Examples of donor atoms having one proton are -OH, -SH and -NH-.

Examples of donor atoms having more than one proton are $-NH_2$, $[-NH_3]-$ and $[-NH_2]^{1+}$

The term hydrogen bonding acceptor moiety refers to a chemical structure containing a suitable hydrogen bond acceptor atom. Examples of acceptor atoms include fluorine, oxygen, sulfur and nitrogen.

The term stacking interaction refers to the favorable attractive interactions between two aromatic ring systems, wherein the two rings are juxtaposed such that they are oriented either face-to-face, perpendicular or at an intermediate angle to each other.

Face-to-face stacking interactions are usually between 3.5-4.5 Ångstrom. Face-edge stackings are usually to be between 3.5 and 4 Å. Most aromatic protein interactions involve separation distances of 3.6 to 3.8 Ångstrom. Fully stacked interactions are not usually observed. Most common are staggered stacked structures with tilted rings. Perpendicular stacking may be face-edge or cogwheel. Both are common.

(Protein-protein recognition via side-chain interactions; Thornton et al.; Biochemical society transactions.; 927-930 (1988)).

The term salt bridge refers to the non-covalent attractive interaction between a positively charged moiety (P) and a negatively charged moiety (N) when the distance between the centers of mass of P and N is between 2 and 6 Angstroms. In calculating the center of mass, atoms which may contain a formal charge and atoms immediately adjacent to these are included. For example, a salt bridge may be formed between the positively charged guanidinium side chain of an arginine residue and the negatively charged carboxylate side chain of a glutamate residue. Salt bridges are well known in medicinal chemistry (L. Stryer, Biochemistr , Freeman, San Francisco, (1975); K.A. Dill, Dominant Forces in Protein Folding, Biochemistry, 29, No. 31, pp. 7133- 7155, (1990)) .

The term center of mass refers to a point in three-dimensional space that represents a weighted average position of the masses that make up an object.

In order to form a desired number of binding interactions with the first binding site, the compound preferably has a binding domain no longer than about 35 Ångstrom long (the length of the first binding groove). Typically compounds will be, for example, 5-30, 5-25, 5-15, 10-15 Å in length.

In order to form a desired number of binding interactions with the second binding site, the compound preferably has a binding domain that can fit into an area of about 30 by 30 Ångstrom (the area of the second binding site). In order optimise interactions at this binding site, compounds will typically be, for example, 5-30, 5-25, 5-15, 10-15 Å in length.

The third binding site, the cavity underneath the cradle, is about 9 by 15 Ångstrom so only small binding domains or small molecules will fit in this cavity, for example those that are 5-15, 10-15 Å in length.

A compound of the invention can possess only a single binding domain or can have binding domains enabling it to bind to two or three binding sites.

Compounds exhibiting *Type 2* or *Type 3* activity typically have a binding domain enabling them to bind to the first and/or second and/or third binding sites so as to bring the nucleophilic group into reactive proximity of the sulfenyl amide group. The nucleophilic groups can form part of the scaffold described above or can take the form of substituents attached to the scaffold.

Screening of compounds

In another aspect, in place of *in silico* methods, high or low throughput screening of compounds to select compounds with binding activity may be undertaken, and those compounds which show binding activity may be selected as possible candidate modulators, and further crystallized with PTP1B sulfenyl amide (e.g. by co-crystallization or by soaking) for X-ray analysis. The resulting X-ray structure may be compared with that of Table 1 or Table 2 for a variety of purposes. The screen may utilise any of the assays detailed below.

Assays for Screening for Active Compounds

Compounds may be identified in high-throughput or low-throughput screening as outlined above, utilizing the assays detailed below. Compounds screened may include those available from commercially available sources, compounds generated by standard synthetic chemistry methods, or those that are part of a corporate compound collection.

Alternatively, once a candidate inhibitor compound has been identified, for example by computer based rational drug design techniques as described above, the compounds are synthesized and tested. Whether or not the compounds are inhibitors of the PTP sulfenyl amide can be determined by one of a number of assays. Consequently, all the methods of compound design and identification above (e.g. *in silico* analysis, ligand-sulfenyl amide PTP structure determination etc) preferably further comprise the further steps of:

obtaining or synthesising the candidate modulator; and

contacting the candidate modulator with PTP1B sulfenyl amide to determine the ability of the candidate modulator to interact with PTP1B sulfenyl amide.

For example, in one assay, the oxidized form (sulfenyl amide form) of a recombinant or extracted protein tyrosine phosphatase is incubated with a candidate binding compound and a determination is made as to whether the compound is able to interact with the oxidized (sulfenyl amide) form of the protein tyrosine phosphatase.

Such assays require the formation of the oxidized form of a protein tyrosine phosphatase. The oxidized form can be produced by incubating the protein tyrosine phosphatase in the presence of oxidizing agents such as a reactive oxygen species in a cellular environment [24, 25], organic peracids e.g. MCPBA, peroxides e.g. hydrogen peroxide [24, 25] or compound(s) as described in the examples below.

The assay can be a binding assay. Such a binding assay can be competitive or non-competitive and can accommodate the screening of a large number of compounds to determine if the compounds are capable of binding to the oxidized protein tyrosine phosphatase. Subsequently other assays can be carried out with compounds found to bind to determine the mode of binding of these compounds.

Alternatively, the assay can be a functional assay that identifies compounds that trap the oxidized form of the protein tyrosine phosphatase and so change its ability to regain its functional activity on reduction. Such an assay can involve incubating potential trapping compounds with the oxidized form of the protein tyrosine phosphatase and determining if protein tyrosine phosphatase activity can be regained upon reduction.

In a further alternative, the assay can be cell-based assay for identifying compounds which modulate the cell-based activity of a protein tyrosine phosphatase, through binding to the oxidized form of protein tyrosine phosphatases in cells.

Particularly preferred types of assays include binding assays, functional assays and cell-based assays, which may be performed as follows:

Binding assays

Purified, oxidized protein tyrosine phosphatases can be used for binding studies. Oxidized protein tyrosine phosphatase can be used in conventional filter-binding assays or in a high throughput scintillation proximity-type binding assay to detect binding of a radio-labelled ligand and its displacement by compounds which compete for the binding site. Radioactivity can be measured with a Packard Topcount or similar instrumentation capable of making rapid measurements for 96-, 384- or 1536-well microtitre plate formats.

Binding to oxidized protein tyrosine phosphatases could also be measured using a fluorescently labelled ligand, which could be displaced by compounds, competing for the binding site. Binding could be detected by fluorescent polarisation methods using an instrument such as the Packard Fusion reader to monitor fluorescence in 96-, 384 or 1536-well microtitre plate formats.

Another method for studying the binding of compounds to the oxidized protein tyrosine phosphatase makes use of a surface plasmon resonance effect, measured by a Biacore instrument. Oxidized protein tyrosine phosphatase could be attached to the biosensor chip of a Biacore and binding of test compounds could be monitored. Examples of the use of the surface plasmon resonance effect may be found in Parsons et al (1995) *Nucleic Acids Res.* **23**, 211-216 and Parsons et al (1997) *Anal. Biochem.***254(1)**, 82-87.

Binding of test compounds to an oxidized protein tyrosine phosphatase could also be monitored using NMR techniques. The difference between NMR spectra of a test compound with and without the oxidized protein tyrosine phosphatase could be analysed to determine if the compound bound the protein tyrosine phosphatase. Competition between test compounds and a known ligand for a binding site on the protein tyrosine phosphatase could also be monitored in this way.

Preferred compounds are those that have a Kd value of less than 1mM, more preferably less than 1uM and most preferably less than 100nM. The term "Kd" is used herein in its normal sense to mean the dissociation constant, which describes

the ratio of the concentrations at equilibrium between the free individual components and the complex formed. For a complex between two components A and B, Kd = [A][B]/[AB].

Functional assays

The oxidized form of a protein tyrosine phosphatase is inactive, but can be reactivated by reduction. An example of a functional assay to monitor compounds that trap the oxidized form of the protein tyrosine phosphatase could involve measuring the time taken for an oxidized form of a protein tyrosine phosphatase to regain activity in the presence of the candidate inhibitor under reducing conditions.

Candidate trapping compounds could then be screened against the oxidized form of the enzyme, by incubating candidate inhibitors and enzyme for a period of time and then adding a reducing agent such as DTT or glutathione. The activity of the enzyme could then be monitored at time intervals after this addition of reducing agent. Enzyme which has been trapped in the oxidized form by candidate inhibitors should take longer to regain activity than enzyme that has not been trapped. Time taken to regain activity could be measured against controls containing no test compound and so correlated to potency of the inhibitor.

Assays for monitoring the activity of protein tyrosine phosphatases have been described in the literature and can use known substrates such as p-nitrophenyl phosphate or phosphorylated peptides (Hoppe et al., 1994, Eur. J. Biochem., 223, 1069-1077; Bleasdale et al., 2001, Biochemistry, 40, 5642-5654; Wang et al., 1999, Biochim Biophys Acta, 1431, 14-23). Assays can be performed in 96- or 384- well microtitre format using a Molecular Devices Spectramax plate reader, allowing screening of a large number of compounds. The dephosphorylation of p-nitrophenyl phosphate by a PTP can be monitored be an increase in absorbance at 405nm. The dephosphorylation of a phosphorylated peptide can be monitored by measuring phosphate release by the malachite green method.

Cell-based Assays

Compounds can also be screened in cell-based assays, specific to the protein tyrosine phosphatase of interest.

Compounds that affect PTP1B can be screened using assays that monitor the effects of insulin on cells. Examples of such assays are as follows:

Cells such as 3T3-L1 can be differentiated into adipocytes and induced to be insulin resistant. Effect of compounds on glucose transport into these cells can be monitored by measuring the rate of uptake of 2-[^{3}H]deoxyglucose when the cells are stimulated by insulin.

Another cell-based assay that can be used to monitor effects of compounds on ptp1b is an assessment of insulin receptor tyrosine kinase activity. In this case the tyrosine kinase activity of the insulin receptor captured from cells, e.g. 3T3-L1, treated with test compounds is measured. Tyrosine kinase activity can be measured using a peptide substrate and [γ^{33}P]-ATP.

A further assay involves monitoring the tyrosine phosphorylation of insulin signalling molecules in cells that have been treated with insulin and test compounds. Phosphorylation of molecules can be detected for example by Western blotting cell extracts using monoclonal antibodies (Bleasdale et al., 2001, Biochemistry, 40, 5642-5654).

Preferred compounds of the invention are those that have IC_{50} values in a cellular assay of less than 1uM, more preferably less than 100nM and most preferably less than 10nM.

Pharmaceutical Formulations

The compounds of the invention can be presented in the form of pharmaceutical compositions.

In another aspect, therefore, the invention provides a pharmaceutical composition comprising a compound that binds to protein tyrosine phosphatase sulfenyl amide

to prevent or inhibit conversion of the protein tyrosine phosphatase sulfenyl amide to an active reduced form of the protein tyrosine phosphatase.

The pharmaceutical compositions can be in any form suitable for oral, parenteral, topical, intranasal, intra-articular, ophthalmic, otic, rectal, intra-vaginal, or transdermal administration. Where the compositions are intended for parenteral administration, they can be formulated for intravenous, intramuscular or subcutaneous administration.

Pharmaceutical dosage forms suitable for oral administration include tablets, capsules, caplets, pills, lozenges, syrups, solutions, powders, granules, elixirs and suspensions, sublingual tablets, wafers or patches and buccal patches.

Pharmaceutical compositions containing compounds of the invention can be formulated in accordance with known techniques, see for example, Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, PA, USA.

Thus, tablet compositions can contain a unit dosage of active compound together with an inert diluent or carrier such as a sugar or sugar alcohol, eg; lactose, sucrose, sorbitol or mannitol; and/or a non-sugar derived diluent such as sodium carbonate, calcium phosphate, calcium carbonate, or a celluloses or derivative thereof such as methyl cellulose, ethyl cellulose, hydroxypropyl methyl cellulose, and starches such as corn starch. Tablets may also contain such standard ingredients as binding and granulating agents agents such as polyvinylpyrrolidone, disintegrants (e.g. swellable crosslinked polymers such as crosslinked carboxymethylcellulose), lubricating agents (e.g. stearates), preservatives (e.g. parabens), antioxidants (e.g. BHT), buffering agents (for example phosphate or citrate buffers), and effervescent agents such as citrate/bicarbonate mixtures. Such excipients are well known and do not need to be discussed in detail here.

Capsule formulations may be of the hard gelatin or soft gelatin variety and can contain the active component in solid, semi-solid, or liquid form. Gelatin capsules can be formed from animal gelatin or synthetic or plant derived equivalents thereof.

The solid dosage forms (eg; tablets, capsules etc.) can be coated or un-coated, but typically have a coating, for example a protective film coating (e.g. a wax or varnish) or a release controlling coating. The coating (e.g. a Eudragit ™ type polymer) can be designed to release the active component at a desired location within the gastro-intestinal tract. Thus, the coating can be selected so as to degrade under certain pH conditions within the gastrointestinal tract, thereby selectively release the compound in the stomach or in the ileum or duodenum.

Instead of, or in addition to, a coating, the drug can be presented in a solid matrix comprising a release controlling agent, for example a release delaying agent which may be adapted to selectively release the compound under conditions of varying acidity or alkalinity in the gastrointestinal tract. Alternatively, the matrix material or release retarding coating can take the form of an erodible polymer (e.g. a maleic anhydride polymer) which is substantially continuously eroded as the dosage form passes through the gastrointestinal tract.

Compositions for topical use include ointments, creams, sprays, patches, gels, liquid drops and inserts (for example intraocular inserts). Such compositions can be formulated in accordance with known methods.

Compositions for parenteral administration are typically presented as sterile aqueous or oily solutions or fine suspensions, or may be provided in finely divided sterile powder form for making up extemporaneously with sterile water for injection.

Examples of formulations for rectal or intra-vaginal administration include pessaries and suppositories which may be, for example, formed from a shaped moldable or waxy material containing the active compound.

Compositions for administration by inhalation may take the form of inhalable powder compositions or liquid or powder sprays, and can be administrated in standard form using powder inhaler devices or aerosol dispensing devices. Such devices are well known. For administration by inhalation, the powdered

formulations typically comprise the active compound together with an inert solid powdered diluent such as lactose.

The compounds of the invention will generally be presented in unit dosage form and, as such, will typically contain sufficient compound to provide a desired level of biological activity. For example, a formulation intended for oral administration may contain from 0.1 milligrams to 2 grams of active ingredient, more usually from 10 milligrams to 1 gram, for example, 50 milligrams to 500 milligrams. The active compound will be administered to a patient in need thereof (for example a human or animal patient) in an amount sufficient to achieve the desired therapeutic effect.

In another aspect, the invention provides a method of preparing a composition comprising (a) identifying a the PTP sulfenyl amide modulator molecule (which may thus be termed a lead compound) by a method of any one of the other aspects of the invention disclosed herein and admixing the molecule with a carrier.

Also provided is a method of preparing a composition comprising (a) identifying a the PTP sulfenyl amide modulator molecule (which may thus be termed a lead compound) by a method of any one of the other aspects of the invention disclosed herein and admixing an optimised structure of the modulator molecule with a carrier.

The invention further provides a process for producing a medicament, pharmaceutical composition or drug, the process comprising: (a) identifying a the PTP sulfenyl amide modulator molecule (which may thus be termed a lead compound) by a method of any one of the other aspects of the invention disclosed herein; and (b) preparing a medicament, pharmaceutical composition or drug containing the modulator molecule.

A further aspect of the present invention provides a method for preparing a medicament, pharmaceutical composition or drug, the method comprising: (a) identifying a the PTP sulfenyl amide modulator molecule (which may thus be termed a lead compound) by a method of any one of the other aspects of the

invention disclosed herein; (b) optimising the structure of the modulator molecule; and (c) preparing a medicament, pharmaceutical composition or drug containing the optimised modulator molecule.

The above-described processes of the invention may be iterative in that the modified compound may itself be the basis for further compound design. Detailed structural information can be obtained about the binding of the candidate modulator to PTP sulfenyl amide , and in the light of this information adjustments can be made to the structure or functionality of the candidate modulator, e.g. to improve binding to the binding cavity or cavities. The above steps may be repeated and re-repeated as necessary.

By "optimising the structure" we mean e.g. adding molecular scaffolding, adding or varying functional groups, or connecting the molecule with other molecules (e.g. using a fragment linking approach) such that the chemical structure of the modulator molecule is changed while its original modulating functionality is maintained or enhanced. Such optimisation is regularly undertaken during drug development programmes to e.g. enhance potency, promote pharmacological acceptability, increase chemical stability etc. of lead compounds.

Modifications typically will be those conventional in the art known to the skilled medicinal chemist, and will include, for example, substitutions or removal of groups containing residues which interact with the amino acid side chain groups of a the PTP sulfenyl amide structure of the invention. For example, the replacements may include the addition or removal of groups in order to decrease or increase the charge of a group in a test compound, the replacement of a charge group with a group of the opposite charge, or the replacement of a hydrophobic group with a hydrophilic group or vice versa. It will be understood that these are only examples of the type of substitutions considered by medicinal chemists in the development of new pharmaceutical compounds and other modifications may be made, depending upon the nature of the starting compound and its activity.

Methods of Treatment

It is envisaged that the compounds of the invention will be useful in the prophylaxis or treatment of a range of disease states or conditions mediated by protein tyrosine phosphatases. Examples of such disease states and conditions are set out above and include the treatment of cancers, diabetes (diabetes type I and II) obesity, autoimmune diseases, acute and chronic inflammation, rheumatoid arthritis, osteoporosis, proliferative disorders including various forms of cancer, growth disorders and hypertension

Compounds of the invention are generally administered to a subject in need of such administration, for example a human or animal patient, preferably a human. The compounds will typically be administered in amounts that are therapeutically or prophylactically useful and which generally are non-toxic. However, in certain situations (for example in the case of life threatening diseases), the benefits of administering a compound of the invention may outweigh the disadvantages of any toxic effects or side effects, in which case it may be considered desirable to administer compounds in amounts that are associated with a degree of toxicity.

A typical daily dose of the compound can be in the range from 100 picograms to 100 milligrams per kilogram of body weight, more typically 10 nanograms to 10 milligrams per kilogram of bodyweight although higher or lower doses may be administered where required. Ultimately, the quantity of compound administered will be commensurate with the nature of the disease or physiological condition being treated and will be at the discretion of the physician.

The compounds of the invention can be administered as the sole therapeutic agent or they can be administered in combination therapy with one of more other compounds for treatment of a particular disease state, for example a neoplastic disease such as a cancer as hereinbefore defined.

EXAMPLES

The invention will now be illustrated in greater detail by reference to the specific embodiments described in the following non-limiting examples.

EXAMPLE 1

PTP1B Expression, Purification, Crystallisation and Structure Determination

Expression, purification and crystallisation of the catalytic domain of PTP1B (residues 1-321) were based on literature conditions – see Barford *et al.* [20], the entire disclosure in which is incorporated herein by reference.

PTP1B Expression, Purification and Crystallization Protocol

Using the DNA sequence of human PTP1B (Genbank nm_002827), a fragment encoding the N-terminal 321 residues was generated and cloned into the expression vector Pet19b (Novagen) at the Nco1 site enabling the initiation of translation at Met1. Primers used to generate the plasmid were:

5'-TTTTCCATGGAGATGGAAAAGGAGTTCG-3' (SEQ.ID. NO: 1)

5'-TTTTCCATGGCTAATTGTGTGGCTCCAGGATTCG-3'. (SEQ.ID. NO: 2)

E.coli bl21 (de3) cells transformed with Pet19b-PTP1B were grown overnight at 37°C in LB medium plus 100μg ampicillin/ml. Typically, 10mls of this overnight culture was used to inoculate 1 litre of LB plus 100μg ampicillin/ml. Cultures were grown at 37°C for 3 hours prior to induction by addition of isopropyl-thio-β-d-galactopyranoside (IPTG) to a final concentration of 1mM. The cultures were grown for a further 3 hours before being harvested by centrifugation.

All purification steps were performed at 4°C and all buffers unless stated otherwise contained a 1/1000 dilution of protease inhibitor cocktail III (Calbiochem).

Bacterial pellets were resuspended on ice in 20mM imidazole, pH7.5, 1mM EDTA, 3mM DTT, 10% (v/v) glycerol and lysed by sonication (2 mins, 20 second pulses). The lysed cells were incubated with DNAase 1 (Sigma) for 10 minutes at 4°C. Following this, the lysate was clarified by centrifugation at 25,000 rpm for 30 minutes. Protein was applied to a Q-sepharose fast flow column incorporated into an Akta fplc system (Amersham Biosciences) at a flow rate of 4ml/min. a linear salt gradient (0-0.5m NaCl in 20mM imidazole, pH7.5, 1mM EDTA, 3mM DTT, 10% (v/v) glycerol) was applied to the column and PTP1B eluted at ~300mM NaCl.

Fractions containing PTP1B were pooled and buffer exchanged using a 26/10 desalting column (Amersham Biosciences) pre-equilibrated in 25mM NaH_2PO_4 pH 6.5, 1mM EDTA, 3mM DTT, 10% (v/v) glycerol. PTP1B fractions were applied to a 10/10 mono s column previously equilibrated in 25mM NaH_2PO_4 pH 6.5, 1mM EDTA, 3mM DTT, 10% (v/v) glycerol. Protein fractions were eluted by applying a linear salt gradient (0-0.5m NaCl) to the column with PTP1B eluting at ~75mM NaCl. PTP1B was buffer exchanged into 10mM Tris pH7.5, 25mM NaCl, 0.2mM EDTA and 3mM DTT. Protein purity was assessed by SDS PAGE and was observed to be >95% pure. This protein was subsequently concentrated to 10mg/ml and used for crystallisation.

Using the hanging drop method (Crystallization of nucleic acids and proteins. A practical approach. A. Ducruix and R. Giege. Oxford University press 1999. and Principles of Protein X-ray Crystallography. Jan Drenth. Springer Verlag 1994.), PTP1B crystals were grown at 4°C from 4μl drops (1:1 ratio protein:reservoir solution) and equilibrated against 1ml reservoir solution consisting of 12-18% (v/v) PEG 4000, 0.1 m HEPES (pH 7.5) and 0.2 M magnesium acetate.

Method for assaying PTP1B activity:

PTP1B enzyme activity was assayed by measuring the dephosphorylation of p-nitrophenyl phosphate to p-nitrophenol. The reaction was monitored by following the increase in absorbance at 405 nm as p-nitrophenol was produced. Standard assays typically contained 0.25 mM p-nitrophenyl phosphate substrate and 25 nM PTP1B enzyme in 50 mM HEPES, pH 6.5, 1 mM DTT, 1 mM EDTA, 0.01% CHAPS buffer. Assays were carried out in Costar 3696 half-area plates in an assay volume of 100ul on a Spectramax plate reader (Molecular Devices). Reactions were typically monitored at 20 second intervals for 30 minutes. For kinetic measurements of km the concentration of the p-nitrophenyl phosphate substrate was varied between 31 uM and 5 mM.

Activity of PTP1B was also monitored by measuring the phosphate produced in the reaction. Standard assays were set up as described above, except that 50ul of malachite green reagent was added to quench the reaction and the absorbance at

620 nm was then measured on a Spectramax plate reader (Molecular Devices) to determine the amount of phosphate produced. Malachite green reagent is made from 0.2% w/v malachite green and 4.2% w/v ammonium molybdate mixed in a ratio of 3:1.

For overnight soaking experiments crystals were transferred into a standard mother liquor containing 16% PEG 4000, 0.1 M HEPES (pH 7.5), 0.2 M magnesium acetate, 10 mM DTT and the compound of interest (See Table 3 below).

All data were collected at 100 K. Data sets of sulfenic- sulfinic- and sulfonic acid PTP1B derivatives were automatically collected on a Jupiter140 CCD detector mounted on a RU3HR rotating anode generator equipped with an ACTOR sample-changing robot (RigakuMSC, The Woodlands Tx, USA). They were processed and scaled using D*TREK[21] and converted to structure factors using programs from the CCP4 suite[22].

Oxidation of Cys215 to the sulfenyl-amide derivative was carried out by soaking crystals for approximately 24 hours in mother liquor without DTT, but containing 100 mM 2-phenyl-isoxazolidine-3,5-dione. Data were collected at station 14.1 (SRS, Daresbury) and processed and scaled using MOSFLM/SCALA[22].

Reversibility of the sulfenyl-amide derivative was checked by first soaking two crystals in 100 mM 2-phenyl-isoxazolidine-3,5-dione for 24 hours. Sulfenyl-amide formation was confirmed by an in-house data set of one of the crystals. After back soaking for 24 hours in mother liquor containing 20 mM reduced glutathione, data collected from the other crystal confirmed the active site in its native conformation.

All results were evaluated using the graphics programs QUANTA (Accelrys, San Diego CA, USA) and Astexviewer™[, 23]. Data collection statistics are summarised in Table 2. Initial refinement was always carried out using the CCP4-based Astex automatic refinement scripts, followed by rounds of positional and B-factor refinement with REFMAC5[22] alternated with manual rebuilding steps using QUANTA.

Monomer libraries for the different oxidation states were generated using REFMAC5 in combination with the monomer sketcher of the CCP4GUI[22].

Table 2: Crystallographic data collection and refinement statistics

	Sulfenic acid	Sulfinic acid	Sulfonic acid	Sulfenyl-amide	Back soaking experiment	
					Compound	Glutathione
Data collection Beamline	In-house	In-house	In-house	SRS 14.1	In-house	In-house
λ (Å)	1.54	1.54	1.54	1.488	1.54	1.54
Resolution (Å)	2.3	2.6	2.2	2.2	2.4	2.2
No. Observations	43942	29624	53452	83434	103350	108793
No. Unique reflections	20755	16237	23367	23591	18514	23322
Completeness (%) *	96.0 (94.9)	95.9 (95.3)	96.0 (86.9)	98.9 (97.4)	99.8 (100)	100 (100)
Rmerge[1,*]	0.092 (0.25)	0.172 (0.37)	0.060 (0.252)	0.050 (0.26)	0.078 (0.273)	0.054 (0.32)
I/σ<I>*	7.3 (2.8)	4.6 (1.9)	11.2 (4.3)	7.8 (2.8)	8.4 (2.8)	12.9 (2.2)
Refinement Rcryst/Rfree	0.187/ 0.248	0.204/ 0.263	0.202/ 0.242	0.243/ 0.283	0.215/ 0.275	0.228/ 0.277
Rmsd Bond lengths (Å)	0.013	0.018	0.012	0.009	0.006	0.006
Rmsd Bond angles (°)	1.4	1.7	1.3	1.4	1.3	1.3

*Numbers in parentheses indicate the highest shell values

.[1]Rmerge = $\Sigma_h\Sigma_i|I(h,i)-\langle I\rangle(h)|\Sigma hSi\langle I\rangle(h)$; I(h,i) is the scaled intensity of the ith observation of reflection h and $\langle I\rangle(h)$ is the mean value. Summation is over all measurements.

Rcryst =$\Sigma_{hkl,work}||F_{obs}|-k|F_{calc}||/\Sigma hkl|F_{obs}I$, where Fobs and Fcalc are the observed and calculated structure factors, k is a weighting factor and work denotes the working set of 95% of the reflections used in the refinement.

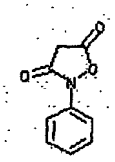
Rfree=$\Sigma_{hkl,test}||F_{obs}|-k|F_{calc}||/\Sigma_{hkl}|F_{obs}|$, where Fobs and Fcalc are the observed and calculated structure factors, k is a weighting factor and test denotes the test set of 5% of the reflections used in cross validation of the refinement.

λ, refers to wavelength, Rmsd to root mean square deviations.

TABLE 3

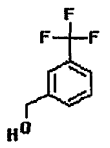
Compounds Used in Soaking Experiments

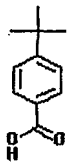
Structure of 2-Phenyl-isoxazolidine-3,5-dione:

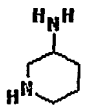


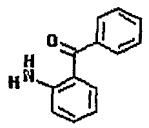
Composition of cocktails used in soaking experiments:

Cocktail composition used in the soaking experiment resulting in the sulfenic acid (Cys-SOH) PTP1B derivative:



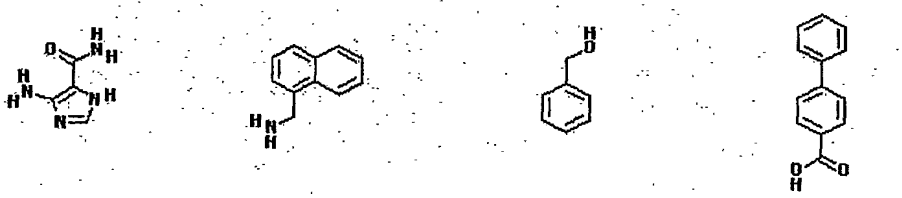






Cocktail composition used in the soaking experiment resulting in the sulfinic acid (Cys-SO2H) PTP1B derivative:

Cocktail composition used in the soaking experiment resulting in the sulfonic acid (Cys-SO3H) PTP1B derivative:



PHARMACEUTICAL FORMULATIONS

EXAMPLE 2

(i) Tablet Formulation

A tablet composition containing a compound of the invention is prepared by mixing 50mg of the compound with 197mg of lactose (BP) as diluent, and 3mg magnesium stearate as a lubricant and compressing to form a tablet in known manner.

(ii) Capsule Formulation

A capsule formulation is prepared by mixing 100mg of a compound of the invention with 100mg lactose and filling the resulting mixture into standard opaque hard gelatin capsules.

Equivalents

It will readily be apparent that numerous modifications and alterations may be made to the specific embodiments of the invention described above without departing from the principles underlying the invention. All such modifications and alterations are intended to be embraced by this application.

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The disclosures of all papers, articles and documents referred to in this application, including the papers and articles numbered 1 to 27 above, are incorporated herein by reference in their entirety.

TABLE 1

Unit cell dimensions:

a = 87.686 Å, b = 87.686 Å, c = 103.721 Å, α = 90.00°, β = 90.00°, γ = 120.00°

Space group:

$P3_1$ 2 1

Table 1

ATOM	1	N	GLU	A	2	17.300	16.060	47.467	1.00	63.20
ATOM	2	CA	GLU	A	2	18.497	16.936	47.513	1.00	61.62
ATOM	3	C	GLU	A	2	19.027	17.081	48.938	1.00	61.51
ATOM	4	O	GLU	A	2	18.389	16.661	49.905	1.00	60.93
ATOM	5	CB	GLU	A	2	18.218	18.300	46.856	1.00	61.28
ATOM	6	CG	GLU	A	2	18.055	19.504	47.780	1.00	61.69
ATOM	7	CD	GLU	A	2	18.744	20.732	47.230	1.00	66.10
ATOM	8	OE1	GLU	A	2	18.034	21.666	46.811	1.00	66.32
ATOM	9	OE2	GLU	A	2	20.002	20.766	47.202	1.00	74.14
ATOM	10	N	MET	A	3	20.191	17.713	49.043	1.00	60.00
ATOM	11	CA	MET	A	3	21.011	17.652	50.240	1.00	57.25
ATOM	12	C	MET	A	3	20.614	18.678	51.265	1.00	55.29
ATOM	13	O	MET	A	3	20.747	18.412	52.452	1.00	50.01
ATOM	14	CB	MET	A	3	22.479	17.882	49.882	1.00	55.54
ATOM	15	CG	MET	A	3	23.423	17.093	50.752	1.00	55.32
ATOM	16	SD	MET	A	3	25.071	17.182	50.098	1.00	54.46
ATOM	17	CE	MET	A	3	25.773	18.277	51.201	1.00	54.00
ATOM	18	N	GLU	A	4	20.198	19.858	50.800	1.00	54.87
ATOM	19	CA	GLU	A	4	19.740	20.939	51.680	1.00	58.22
ATOM	20	C	GLU	A	4	18.449	20.513	52.380	1.00	60.58
ATOM	21	O	GLU	A	4	18.315	20.650	53.597	1.00	59.53
ATOM	22	CB	GLU	A	4	19.514	22.229	50.883	1.00	58.04
ATOM	23	CG	GLU	A	4	19.295	23.466	51.743	1.00	58.46
ATOM	24	CD	GLU	A	4	19.539	24.760	50.984	1.00	61.10
ATOM	25	OE1	GLU	A	4	19.208	24.828	49.782	1.00	65.91
ATOM	26	OE2	GLU	A	4	20.064	25.717	51.587	1.00	62.36
ATOM	27	N	LYS	A	5	17.514	19.985	51.594	1.00	63.68
ATOM	28	CA	LYS	A	5	16.304	19.358	52.121	1.00	65.50
ATOM	29	C	LYS	A	5	16.669	18.372	53.236	1.00	64.36
ATOM	30	O	LYS	A	5	16.160	18.486	54.354	1.00	62.53
ATOM	31	CB	LYS	A	5	15.546	18.637	50.994	1.00	67.62
ATOM	32	CG	LYS	A	5	14.134	18.140	51.362	1.00	72.06
ATOM	33	CD	LYS	A	5	13.886	16.663	50.965	1.00	74.03
ATOM	34	CE	LYS	A	5	12.516	16.450	50.305	1.00	75.34
ATOM	35	NZ	LYS	A	5	12.393	17.128	48.976	1.00	74.88
ATOM	36	N	GLU	A	6	17.567	17.434	52.927	1.00	61.33
ATOM	37	CA	GLU	A	6	17.992	16.400	53.876	1.00	60.50
ATOM	38	C	GLU	A	6	18.602	17.026	55.129	1.00	59.07
ATOM	39	O	GLU	A	6	18.240	16.671	56.244	1.00	59.12
ATOM	40	CB	GLU	A	6	19.003	15.439	53.232	1.00	60.37
ATOM	41	CG	GLU	A	6	19.396	14.260	54.116	1.00	60.01
ATOM	42	CD	GLU	A	6	20.566	13.453	53.572	1.00	61.12
ATOM	43	OE1	GLU	A	6	20.848	13.512	52.359	1.00	61.84
ATOM	44	OE2	GLU	A	6	21.205	12.737	54.368	1.00	62.14

ATOM	45	N	PHE	A	7	19.529	17.957	54.927	1.00	57.25
ATOM	46	CA	PHE	A	7	20.140	18.727	56.009	1.00	56.47
ATOM	47	C	PHE	A	7	19.079	19.264	56.981	1.00	58.79
ATOM	48	O	PHE	A	7	19.212	19.105	58.189	1.00	55.70
ATOM	49	CB	PHE	A	7	20.941	19.886	55.407	1.00	54.93
ATOM	50	CG	PHE	A	7	21.692	20.708	56.409	1.00	52.66
ATOM	51	CD1	PHE	A	7	21.264	21.981	56.736	1.00	53.50
ATOM	52	CD2	PHE	A	7	22.852	20.221	56.994	1.00	53.27
ATOM	53	CE1	PHE	A	7	21.967	22.747	57.649	1.00	54.98
ATOM	54	CE2	PHE	A	7	23.560	20.973	57.904	1.00	50.40
ATOM	55	CZ	PHE	A	7	23.126	22.237	58.234	1.00	54.44
ATOM	56	N	GLU	A	8	18.028	19.876	56.433	1.00	59.80
ATOM	57	CA	GLU	A	8	16.966	20.489	57.228	1.00	62.23
ATOM	58	C	GLU	A	8	16.125	19.451	57.962	1.00	61.71
ATOM	59	O	GLU	A	8	15.778	19.648	59.117	1.00	64.03
ATOM	60	CB	GLU	A	8	16.082	21.388	56.351	1.00	63.16
ATOM	61	CG	GLU	A	8	16.657	22.792	56.189	1.00	64.89
ATOM	62	CD	GLU	A	8	16.174	23.521	54.943	1.00	68.05
ATOM	63	OE1	GLU	A	8	15.280	23.002	54.235	1.00	69.31
ATOM	64	OE2	GLU	A	8	16.696	24.631	54.671	1.00	70.62
ATOM	65	N	GLN	A	9	15.823	18.340	57.303	1.00	62.72
ATOM	66	CA	GLN	A	9	15.137	17.223	57.948	1.00	64.42
ATOM	67	C	GLN	A	9	15.898	16.765	59.201	1.00	64.36
ATOM	68	O	GLN	A	9	15.284	16.393	60.191	1.00	63.25
ATOM	69	CB	GLN	A	9	14.961	16.052	56.961	1.00	67.37
ATOM	70	CG	GLN	A	9	14.474	14.725	57.579	1.00	71.31
ATOM	71	CD	GLN	A	9	15.601	13.710	57.822	1.00	75.81
ATOM	72	OE1	GLN	A	9	15.778	13.226	58.948	1.00	77.61
ATOM	73	NE2	GLN	A	9	16.353	13.384	56.768	1.00	77.69
ATOM	74	N	ILE	A	10	17.230	16.802	59.152	1.00	63.29
ATOM	75	CA	ILE	A	10	18.070	16.360	60.264	1.00	60.87
ATOM	76	C	ILE	A	10	18.214	17.468	61.297	1.00	58.42
ATOM	77	O	ILE	A	10	18.294	17.193	62.482	1.00	56.02
ATOM	78	CB	ILE	A	10	19.477	15.920	59.760	1.00	62.50
ATOM	79	CG1	ILE	A	10	19.366	14.830	58.693	1.00	61.57
ATOM	80	CG2	ILE	A	10	20.341	15.400	60.909	1.00	61.51
ATOM	81	CD1	ILE	A	10	20.531	14.838	57.723	1.00	62.38
ATOM	82	N	ASP	A	11	18.242	18.717	60.846	1.00	57.74
ATOM	83	CA	ASP	A	11	18.500	19.839	61.740	1.00	60.17
ATOM	84	C	ASP	A	11	17.331	20.064	62.715	1.00	66.19
ATOM	85	O	ASP	A	11	17.542	20.152	63.934	1.00	67.55
ATOM	86	CB	ASP	A	11	18.810	21.119	60.946	1.00	57.92
ATOM	87	CG	ASP	A	11	20.141	21.745	61.337	1.00	57.04
ATOM	88	OD1	ASP	A	11	20.949	21.072	61.995	1.00	51.82
ATOM	89	OD2	ASP	A	11	20.474	22.910	61.039	1.00	58.59
ATOM	90	N	LYS	A	12	16.111	20.143	62.177	1.00	69.33
ATOM	91	CA	LYS	A	12	14.906	20.286	62.998	1.00	71.11
ATOM	92	C	LYS	A	12	14.553	18.991	63.749	1.00	70.45
ATOM	93	O	LYS	A	12	14.050	19.045	64.870	1.00	70.33
ATOM	94	CB	LYS	A	12	13.709	20.810	62.172	1.00	72.97
ATOM	95	CG	LYS	A	12	13.231	19.924	61.005	1.00	74.96
ATOM	96	CD	LYS	A	12	11.701	19.746	60.978	1.00	76.87
ATOM	97	CE	LYS	A	12	10.968	20.982	60.455	1.00	77.63
ATOM	98	NZ	LYS	A	12	9.535	20.997	60.876	1.00	77.36
ATOM	99	N	SER	A	13	14.846	17.838	63.147	1.00	70.77
ATOM	100	CA	SER	A	13	14.634	16.538	63.802	1.00	69.85
ATOM	101	C	SER	A	13	15.676	16.234	64.886	1.00	70.13
ATOM	102	O	SER	A	13	15.508	15.281	65.651	1.00	70.93

ATOM	103	CB	SER	A	13	14.653	15.408	62.773	1.00	69.58
ATOM	104	OG	SER	A	13	14.288	14.167	63.350	1.00	70.26
ATOM	105	N	GLY	A	14	16.747	17.028	64.942	1.00	69.41
ATOM	106	CA	GLY	A	14	17.810	16.840	65.914	1.00	68.23
ATOM	107	C	GLY	A	14	18.455	15.461	65.892	1.00	67.73
ATOM	108	O	GLY	A	14	18.794	14.929	66.952	1.00	68.22
ATOM	109	N	SER	A	15	18.651	14.896	64.697	1.00	65.75
ATOM	110	CA	SER	A	15	19.148	13.520	64.550	1.00	64.50
ATOM	111	C	SER	A	15	20.604	13.416	64.048	1.00	61.83
ATOM	112	O	SER	A	15	21.027	12.350	63.591	1.00	59.16
ATOM	113	CB	SER	A	15	18.219	12.709	63.634	1.00	64.41
ATOM	114	OG	SER	A	15	17.326	13.550	62.921	1.00	68.90
ATOM	115	N	TRP	A	16	21.377	14.495	64.158	1.00	59.81
ATOM	116	CA	TRP	A	16	22.779	14.466	63.720	1.00	58.20
ATOM	117	C	TRP	A	16	23.563	13.374	64.419	1.00	58.30
ATOM	118	O	TRP	A	16	24.215	12.568	63.768	1.00	56.78
ATOM	119	CB	TRP	A	16	23.458	15.813	63.939	1.00	57.31
ATOM	120	CG	TRP	A	16	23.063	16.794	62.905	1.00	57.69
ATOM	121	CD1	TRP	A	16	22.356	17.937	63.091	1.00	58.78
ATOM	122	CD2	TRP	A	16	23.327	16.707	61.501	1.00	59.24
ATOM	123	NE1	TRP	A	16	22.164	18.576	61.892	1.00	59.34
ATOM	124	CE2	TRP	A	16	22.754	17.841	60.897	1.00	61.47
ATOM	125	CE3	TRP	A	16	23.985	15.774	60.685	1.00	59.52
ATOM	126	CZ2	TRP	A	16	22.818	18.073	59.513	1.00	60.24
ATOM	127	CZ3	TRP	A	16	24.057	16.009	59.318	1.00	56.01
ATOM	128	CH2	TRP	A	16	23.479	17.149	58.749	1.00	57.24
ATOM	129	N	ALA	A	17	23.480	13.340	65.746	1.00	60.14
ATOM	130	CA	ALA	A	17	24.142	12.305	66.538	1.00	58.74
ATOM	131	C	ALA	A	17	23.755	10.901	66.084	1.00	57.85
ATOM	132	O	ALA	A	17	24.603	10.012	66.004	1.00	57.84
ATOM	133	CB	ALA	A	17	23.812	12.490	68.011	1.00	60.75
ATOM	134	N	ALA	A	18	22.473	10.709	65.787	1.00	58.13
ATOM	135	CA	ALA	A	18	21.955	9.394	65.403	1.00	58.42
ATOM	136	C	ALA	A	18	22.355	8.979	63.980	1.00	58.15
ATOM	137	O	ALA	A	18	22.669	7.813	63.731	1.00	55.17
ATOM	138	CB	ALA	A	18	20.442	9.366	65.555	1.00	57.99
ATOM	139	N	ILE	A	19	22.324	9.931	63.049	1.00	59.40
ATOM	140	CA	ILE	A	19	22.723	9.674	61.659	1.00	59.74
ATOM	141	C	ILE	A	19	24.223	9.420	61.620	1.00	56.93
ATOM	142	O	ILE	A	19	24.698	8.520	60.924	1.00	54.95
ATOM	143	CB	ILE	A	19	22.354	10.877	60.730	1.00	61.02
ATOM	144	CG1	ILE	A	19	20.831	10.977	60.537	1.00	61.51
ATOM	145	CG2	ILE	A	19	23.059	10.760	59.375	1.00	61.84
ATOM	146	CD1	ILE	A	19	20.244	9.940	59.571	1.00	62.30
ATOM	147	N	TYR	A	20	24.961	10.220	62.382	1.00	56.23
ATOM	148	CA	TYR	A	20	26.397	10.045	62.497	1.00	55.96
ATOM	149	C	TYR	A	20	26.708	8.642	62.985	1.00	54.08
ATOM	150	O	TYR	A	20	27.584	7.975	62.444	1.00	50.49
ATOM	151	CB	TYR	A	20	27.020	11.083	63.440	1.00	55.69
ATOM	152	CG	TYR	A	20	28.491	10.821	63.664	1.00	57.45
ATOM	153	CD1	TYR	A	20	29.392	10.873	62.604	1.00	58.07
ATOM	154	CD2	TYR	A	20	28.973	10.463	64.916	1.00	56.79
ATOM	155	CE1	TYR	A	20	30.731	10.608	62.791	1.00	57.90
ATOM	156	CE2	TYR	A	20	30.307	10.201	65.110	1.00	57.86
ATOM	157	CZ	TYR	A	20	31.181	10.279	64.045	1.00	56.10
ATOM	158	OH	TYR	A	20	32.501	10.016	64.241	1.00	53.46
ATOM	159	N	GLN	A	21	25.965	8.189	63.991	1.00	55.74
ATOM	160	CA	GLN	A	21	26.229	6.890	64.588	1.00	57.04

ATOM	161	C	GLN	A	21	25.867	5.725	63.673	1.00	54.95
ATOM	162	O	GLN	A	21	26.488	4.680	63.776	1.00	56.01
ATOM	163	CB	GLN	A	21	25.547	6.749	65.960	1.00	59.46
ATOM	164	CG	GLN	A	21	26.326	5.856	66.946	1.00	62.63
ATOM	165	CD	GLN	A	21	27.747	6.370	67.254	1.00	64.64
ATOM	166	OE1	GLN	A	21	27.933	7.540	67.624	1.00	65.76
ATOM	167	NE2	GLN	A	21	28.741	5.492	67.106	1.00	64.52
ATOM	168	N	ASP	A	22	24.893	5.891	62.777	1.00	55.58
ATOM	169	CA	ASP	A	22	24.578	4.833	61.807	1.00	58.11
ATOM	170	C	ASP	A	22	25.732	4.660	60.830	1.00	55.90
ATOM	171	O	ASP	A	22	26.113	3.537	60.499	1.00	54.23
ATOM	172	CB	ASP	A	22	23.314	5.143	61.001	1.00	61.30
ATOM	173	CG	ASP	A	22	22.053	5.090	61.833	1.00	67.69
ATOM	174	OD1	ASP	A	22	21.876	4.115	62.604	1.00	71.22
ATOM	175	OD2	ASP	A	22	21.174	5.985	61.769	1.00	71.52
ATOM	176	N	ILE	A	23	26.271	5.783	60.361	1.00	53.69
ATOM	177	CA	ILE	A	23	27.378	5.770	59.408	1.00	53.37
ATOM	178	C	ILE	A	23	28.566	5.069	60.033	1.00	50.71
ATOM	179	O	ILE	A	23	29.214	4.250	59.391	1.00	44.98
ATOM	180	CB	ILE	A	23	27.768	7.215	58.997	1.00	53.19
ATOM	181	CG1	ILE	A	23	26.722	7.799	58.054	1.00	53.10
ATOM	182	CG2	ILE	A	23	29.136	7.243	58.315	1.00	54.93
ATOM	183	CD1	ILE	A	23	26.799	9.301	57.933	1.00	55.17
ATOM	184	N	ARG	A	24	28.839	5.401	61.291	1.00	53.62
ATOM	185	CA	ARG	A	24	29.949	4.790	62.027	1.00	58.86
ATOM	186	C	ARG	A	24	29.814	3.265	62.157	1.00	58.90
ATOM	187	O	ARG	A	24	30.803	2.548	62.062	1.00	54.97
ATOM	188	CB	ARG	A	24	30.104	5.425	63.412	1.00	61.20
ATOM	189	CG	ARG	A	24	31.536	5.398	63.933	1.00	67.63
ATOM	190	CD	ARG	A	24	31.711	4.776	65.313	1.00	73.89
ATOM	191	NE	ARG	A	24	31.711	5.781	66.377	1.00	77.54
ATOM	192	CZ	ARG	A	24	31.977	5.523	67.654	1.00	80.87
ATOM	193	NH1	ARG	A	24	32.264	4.285	68.052	1.00	82.17
ATOM	194	NH2	ARG	A	24	31.950	6.509	68.543	1.00	82.16
ATOM	195	N	HIS	A	25	28.593	2.774	62.357	1.00	62.10
ATOM	196	CA	HIS	A	25	28.359	1.330	62.436	1.00	64.65
ATOM	197	C	HIS	A	25	28.473	0.658	61.059	1.00	61.06
ATOM	198	O	HIS	A	25	28.941	-0.480	60.956	1.00	58.40
ATOM	199	CB	HIS	A	25	26.993	1.028	63.070	1.00	67.93
ATOM	200	CG	HIS	A	25	26.859	-0.384	63.559	1.00	74.44
ATOM	201	ND1	HIS	A	25	25.893	-1.248	63.087	1.00	77.50
ATOM	202	CD2	HIS	A	25	27.588	-1.090	64.457	1.00	77.23
ATOM	203	CE1	HIS	A	25	26.026	-2.422	63.680	1.00	78.94
ATOM	204	NE2	HIS	A	25	27.046	-2.352	64.517	1.00	79.41
ATOM	205	N	GLU	A	26	28.059	1.374	60.012	1.00	58.65
ATOM	206	CA	GLU	A	26	28.156	0.890	58.632	1.00	56.89
ATOM	207	C	GLU	A	26	29.616	0.814	58.155	1.00	55.60
ATOM	208	O	GLU	A	26	29.943	0.026	57.270	1.00	52.37
ATOM	209	CB	GLU	A	26	27.372	1.814	57.687	1.00	58.61
ATOM	210	CG	GLU	A	26	25.848	1.721	57.748	1.00	61.50
ATOM	211	CD	GLU	A	26	25.167	2.522	56.631	1.00	64.68
ATOM	212	OE1	GLU	A	26	25.149	2.040	55.469	1.00	66.62
ATOM	213	OE2	GLU	A	26	24.658	3.639	56.901	1.00	62.82
ATOM	214	N	ALA	A	27	30.489	1.625	58.756	1.00	53.91
ATOM	215	CA	ALA	A	27	31.836	1.875	58.225	1.00	53.38
ATOM	216	C	ALA	A	27	32.749	0.659	58.215	1.00	51.05
ATOM	217	O	ALA	A	27	32.577	-0.266	59.007	1.00	54.77
ATOM	218	CB	ALA	A	27	32.502	3.012	58.998	1.00	52.70

ATOM	219	N	SER	A	28	33.744	0.695	57.333	1.00	47.02
ATOM	220	CA	SER	A	28	34.641	-0.446	57.115	1.00	47.65
ATOM	221	C	SER	A	28	35.608	-0.626	58.270	1.00	48.65
ATOM	222	O	SER	A	28	35.990	0.348	58.930	1.00	47.16
ATOM	223	CB	SER	A	28	35.488	-0.260	55.843	1.00	46.74
ATOM	224	OG	SER	A	28	34.741	0.238	54.748	1.00	44.10
ATOM	225	N	ASP	A	29	36.035	-1.866	58.473	1.00	49.97
ATOM	226	CA	ASP	A	29	36.999	-2.195	59.508	1.00	52.38
ATOM	227	C	ASP	A	29	37.986	-3.217	58.977	1.00	49.09
ATOM	228	O	ASP	A	29	37.690	-4.404	58.902	1.00	56.60
ATOM	229	CB	ASP	A	29	36.288	-2.718	60.760	1.00	56.80
ATOM	230	CG	ASP	A	29	37.183	-2.697	61.994	1.00	59.43
ATOM	231	OD1	ASP	A	29	38.114	-1.863	62.046	1.00	62.50
ATOM	232	OD2	ASP	A	29	37.020	-3.471	62.960	1.00	62.02
ATOM	233	N	PHE	A	30	39.161	-2.733	58.606	1.00	44.75
ATOM	234	CA	PHE	A	30	40.168	-3.529	57.925	1.00	41.06
ATOM	235	C	PHE	A	30	41.380	-3.665	58.830	1.00	40.54
ATOM	236	O	PHE	A	30	41.525	-2.882	59.763	1.00	43.29
ATOM	237	CB	PHE	A	30	40.562	-2.828	56.620	1.00	39.31
ATOM	238	CG	PHE	A	30	39.502	-2.878	55.551	1.00	36.76
ATOM	239	CD1	PHE	A	30	39.243	-4.061	54.868	1.00	35.27
ATOM	240	CD2	PHE	A	30	38.781	-1.733	55.203	1.00	32.94
ATOM	241	CE1	PHE	A	30	38.281	-4.114	53.868	1.00	33.02
ATOM	242	CE2	PHE	A	30	37.816	-1.773	54.190	1.00	32.39
ATOM	243	CZ	PHE	A	30	37.562	-2.961	53.519	1.00	34.23
ATOM	244	N	PRO	A	31	42.255	-4.637	58.573	1.00	39.38
ATOM	245	CA	PRO	A	31	43.447	-4.816	59.409	1.00	41.61
ATOM	246	C	PRO	A	31	44.463	-3.686	59.285	1.00	43.42
ATOM	247	O	PRO	A	31	44.527	-3.030	58.242	1.00	43.43
ATOM	248	CB	PRO	A	31	44.075	-6.107	58.875	1.00	40.50
ATOM	249	CG	PRO	A	31	43.576	-6.239	57.495	1.00	40.37
ATOM	250	CD	PRO	A	31	42.181	-5.658	57.516	1.00	40.35
ATOM	251	N	CYS	A	32	45.244	-3.506	60.354	1.00	43.17
ATOM	252	CA	CYS	A	32	46.340	-2.545	60.435	1.00	43.74
ATOM	253	C	CYS	A	32	47.577	-3.203	61.052	1.00	44.00
ATOM	254	O	CYS	A	32	48.220	-2.627	61.924	1.00	41.19
ATOM	255	CB	CYS	A	32	45.937	-1.372	61.325	1.00	42.18
ATOM	256	SG	CYS	A	32	44.513	-0.438	60.792	1.00	40.55
ATOM	257	N	ARG	A	33	47.903	-4.405	60.599	1.00	45.04
ATOM	258	CA	ARG	A	33	48.957	-5.214	61.214	1.00	47.18
ATOM	259	C	ARG	A	33	50.330	-4.574	61.103	1.00	44.66
ATOM	260	O	ARG	A	33	51.142	-4.652	62.029	1.00	43.21
ATOM	261	CB	ARG	A	33	48.993	-6.622	60.597	1.00	50.33
ATOM	262	CG	ARG	A	33	47.642	-7.333	60.664	1.00	55.89
ATOM	263	CD	ARG	A	33	47.679	-8.868	60.565	1.00	61.15
ATOM	264	NE	ARG	A	33	46.343	-9.403	60.854	1.00	65.45
ATOM	265	CZ	ARG	A	33	45.403	-9.700	59.943	1.00	67.05
ATOM	266	NH1	ARG	A	33	44.218	-10.151	60.357	1.00	67.41
ATOM	267	NH2	ARG	A	33	45.630	-9.563	58.634	1.00	64.70
ATOM	268	N	VAL	A	34	50.609	-3.954	59.969	1.00	38.20
ATOM	269	CA	VAL	A	34	51.912	-3.339	59.805	1.00	39.88
ATOM	270	C	VAL	A	34	52.086	-2.196	60.820	1.00	39.12
ATOM	271	O	VAL	A	34	53.167	-2.049	61.400	1.00	35.07
ATOM	272	CB	VAL	A	34	52.157	-2.882	58.373	1.00	40.69
ATOM	273	CG1	VAL	A	34	53.503	-2.189	58.276	1.00	41.70
ATOM	274	CG2	VAL	A	34	52.103	-4.098	57.427	1.00	40.83
ATOM	275	N	ALA	A	35	51.004	-1.443	61.051	1.00	36.64
ATOM	276	CA	ALA	A	35	51.011	-0.297	61.952	1.00	40.93

ATOM	277	C	ALA	A	35	51.190	-0.711	63.411	1.00	42.58
ATOM	278	O	ALA	A	35	51.694	0.073	64.208	1.00	41.51
ATOM	279	CB	ALA	A	35	49.711	0.511	61.814	1.00	38.22
ATOM	280	N	LYS	A	36	50.739	-1.920	63.748	1.00	42.79
ATOM	281	CA	LYS	A	36	50.774	-2.436	65.112	1.00	42.74
ATOM	282	C	LYS	A	36	52.059	-3.216	65.426	1.00	40.53
ATOM	283	O	LYS	A	36	52.229	-3.678	66.545	1.00	41.91
ATOM	284	CB	LYS	A	36	49.539	-3.311	65.388	1.00	45.34
ATOM	285	CG	LYS	A	36	48.189	-2.565	65.347	1.00	48.30
ATOM	286	CD	LYS	A	36	47.948	-1.770	66.633	1.00	53.46
ATOM	287	CE	LYS	A	36	47.424	-0.354	66.388	1.00	53.76
ATOM	288	NZ	LYS	A	36	46.777	0.176	67.615	1.00	52.68
ATOM	289	N	LEU	A	37	52.970	-3.338	64.465	1.00	40.84
ATOM	290	CA	LEU	A	37	54.249	-3.991	64.716	1.00	41.82
ATOM	291	C	LEU	A	37	55.108	-3.186	65.702	1.00	48.37
ATOM	292	O	LEU	A	37	55.166	-1.949	65.624	1.00	47.86
ATOM	293	CB	LEU	A	37	55.032	-4.185	63.436	1.00	40.53
ATOM	294	CG	LEU	A	37	54.415	-5.077	62.365	1.00	43.98
ATOM	295	CD1	LEU	A	37	55.328	-5.082	61.158	1.00	42.81
ATOM	296	CD2	LEU	A	37	54.166	-6.504	62.877	1.00	48.44
ATOM	297	N	PRO	A	38	55.750	-3.880	66.642	1.00	49.83
ATOM	298	CA	PRO	A	38	56.643	-3.226	67.608	1.00	46.21
ATOM	299	C	PRO	A	38	57.711	-2.334	66.992	1.00	43.54
ATOM	300	O	PRO	A	38	57.990	-1.293	67.563	1.00	39.97
ATOM	301	CB	PRO	A	38	57.286	-4.410	68.349	1.00	48.79
ATOM	302	CG	PRO	A	38	56.261	-5.510	68.263	1.00	50.65
ATOM	303	CD	PRO	A	38	55.605	-5.327	66.917	1.00	50.16
ATOM	304	N	LYS	A	39	58.301	-2.700	65.862	1.00	43.10
ATOM	305	CA	LYS	A	39	59.311	-1.831	65.257	1.00	44.66
ATOM	306	C	LYS	A	39	58.752	-0.485	64.732	1.00	44.89
ATOM	307	O	LYS	A	39	59.520	0.417	64.393	1.00	43.74
ATOM	308	CB	LYS	A	39	60.070	-2.552	64.141	1.00	46.32
ATOM	309	CG	LYS	A	39	59.264	-2.891	62.896	1.00	48.76
ATOM	310	CD	LYS	A	39	60.203	-3.220	61.744	1.00	51.08
ATOM	311	CE	LYS	A	39	59.470	-3.894	60.595	1.00	53.07
ATOM	312	NZ	LYS	A	39	60.386	-4.156	59.448	1.00	54.38
ATOM	313	N	ASN	A	40	57.429	-0.368	64.662	1.00	42.04
ATOM	314	CA	ASN	A	40	56.774	0.833	64.148	1.00	43.82
ATOM	315	C	ASN	A	40	56.155	1.692	65.230	1.00	44.28
ATOM	316	O	ASN	A	40	55.560	2.719	64.923	1.00	39.51
ATOM	317	CB	ASN	A	40	55.692	0.449	63.125	1.00	39.92
ATOM	318	CG	ASN	A	40	56.278	-0.081	61.847	1.00	34.23
ATOM	319	OD1	ASN	A	40	57.368	0.324	61.435	1.00	38.32
ATOM	320	ND2	ASN	A	40	55.560	-0.989	61.201	1.00	35.81
ATOM	321	N	LYS	A	41	56.294	1.284	66.490	1.00	45.17
ATOM	322	CA	LYS	A	41	55.645	2.002	67.589	1.00	47.23
ATOM	323	C	LYS	A	41	56.064	3.467	67.635	1.00	42.51
ATOM	324	O	LYS	A	41	55.239	4.324	67.897	1.00	40.36
ATOM	325	CB	LYS	A	41	55.919	1.337	68.949	1.00	52.38
ATOM	326	CG	LYS	A	41	54.780	1.518	69.972	1.00	57.24
ATOM	327	CD	LYS	A	41	55.276	2.101	71.301	1.00	63.21
ATOM	328	CE	LYS	A	41	54.238	1.968	72.427	1.00	64.88
ATOM	329	NZ	LYS	A	41	54.694	2.635	73.696	1.00	66.35
ATOM	330	N	ASN	A	42	57.335	3.746	67.366	1.00	41.10
ATOM	331	CA	ASN	A	42	57.827	5.129	67.386	1.00	44.23
ATOM	332	C	ASN	A	42	57.461	5.950	66.128	1.00	40.34
ATOM	333	O	ASN	A	42	57.751	7.142	66.061	1.00	37.49
ATOM	334	CB	ASN	A	42	59.348	5.198	67.698	1.00	45.89

ATOM	335	CG	ASN	A	42	60.232	4.486	66.650	1.00	54.46
ATOM	336	OD1	ASN	A	42	59.751	3.951	65.641	1.00	60.22
ATOM	337	ND2	ASN	A	42	61.545	4.476	66.906	1.00	57.61
ATOM	338	N	ARG	A	43	56.821	5.308	65.149	1.00	36.12
ATOM	339	CA	ARG	A	43	56.379	5.971	63.923	1.00	32.01
ATOM	340	C	ARG	A	43	54.916	6.387	63.959	1.00	30.04
ATOM	341	O	ARG	A	43	54.437	7.037	63.032	1.00	29.73
ATOM	342	CB	ARG	A	43	56.679	5.111	62.708	1.00	30.74
ATOM	343	CG	ARG	A	43	58.164	4.956	62.499	1.00	28.56
ATOM	344	CD	ARG	A	43	58.527	4.042	61.392	1.00	32.76
ATOM	345	NE	ARG	A	43	59.966	4.062	61.163	1.00	33.60
ATOM	346	CZ	ARG	A	43	60.558	3.850	60.006	1.00	35.25
ATOM	347	NH1	ARG	A	43	59.851	3.602	58.915	1.00	38.60
ATOM	348	NH2	ARG	A	43	61.880	3.888	59.934	1.00	38.43
ATOM	349	N	ASN	A	44	54.236	6.060	65.053	1.00	30.11
ATOM	350	CA	ASN	A	44	52.833	6.357	65.219	1.00	29.93
ATOM	351	C	ASN	A	44	52.574	7.372	66.299	1.00	32.80
ATOM	352	O	ASN	A	44	53.110	7.257	67.387	1.00	30.67
ATOM	353	CB	ASN	A	44	52.074	5.077	65.583	1.00	32.74
ATOM	354	CG	ASN	A	44	51.984	4.121	64.421	1.00	38.06
ATOM	355	OD1	ASN	A	44	51.661	4.522	63.290	1.00	35.12
ATOM	356	ND2	ASN	A	44	52.307	2.860	64.674	1.00	34.92
ATOM	357	N	ARG	A	45	51.693	8.324	66.003	1.00	32.08
ATOM	358	CA	ARG	A	45	51.336	9.386	66.931	1.00	34.13
ATOM	359	C	ARG	A	45	50.227	8.864	67.836	1.00	37.52
ATOM	360	O	ARG	A	45	49.263	8.252	67.367	1.00	32.83
ATOM	361	CB	ARG	A	45	50.906	10.639	66.148	1.00	30.80
ATOM	362	CG	ARG	A	45	50.324	11.778	66.956	1.00	33.11
ATOM	363	CD	ARG	A	45	49.976	13.022	66.097	1.00	31.47
ATOM	364	NE	ARG	A	45	51.175	13.653	65.566	1.00	31.60
ATOM	365	CZ	ARG	A	45	52.045	14.366	66.295	1.00	30.87
ATOM	366	NH1	ARG	A	45	51.844	14.584	67.583	1.00	32.36
ATOM	367	NH2	ARG	A	45	53.126	14.869	65.725	1.00	31.31
ATOM	368	N	TYR	A	46	50.377	9.110	69.136	1.00	42.46
ATOM	369	CA	TYR	A	46	49.474	8.579	70.144	1.00	47.44
ATOM	370	C	TYR	A	46	48.146	9.272	69.956	1.00	48.50
ATOM	371	O	TYR	A	46	48.109	10.419	69.504	1.00	47.96
ATOM	372	CB	TYR	A	46	50.027	8.827	71.560	1.00	50.82
ATOM	373	CG	TYR	A	46	49.268	8.129	72.680	1.00	54.90
ATOM	374	CD1	TYR	A	46	49.341	6.744	72.851	1.00	59.72
ATOM	375	CD2	TYR	A	46	48.488	8.857	73.583	1.00	59.64
ATOM	376	CE1	TYR	A	46	48.652	6.101	73.899	1.00	61.54
ATOM	377	CE2	TYR	A	46	47.795	8.225	74.632	1.00	59.70
ATOM	378	CZ	TYR	A	46	47.883	6.852	74.785	1.00	62.30
ATOM	379	OH	TYR	A	46	47.202	6.232	75.817	1.00	63.70
ATOM	380	N	ARG	A	47	47.062	8.560	70.263	1.00	50.57
ATOM	381	CA	ARG	A	47	45.694	9.060	70.089	1.00	52.62
ATOM	382	C	ARG	A	47	45.345	9.364	68.630	1.00	49.86
ATOM	383	O	ARG	A	47	44.298	9.964	68.353	1.00	52.74
ATOM	384	CB	ARG	A	47	45.430	10.286	70.977	1.00	57.04
ATOM	385	CG	ARG	A	47	45.252	9.948	72.451	1.00	63.95
ATOM	386	CD	ARG	A	47	45.456	11.129	73.399	1.00	67.89
ATOM	387	NE	ARG	A	47	45.300	10.715	74.793	1.00	72.16
ATOM	388	CZ	ARG	A	47	44.134	10.532	75.414	1.00	76.00
ATOM	389	NH1	ARG	A	47	44.121	10.144	76.685	1.00	77.94
ATOM	390	NH2	ARG	A	47	42.980	10.745	74.788	1.00	76.37
ATOM	391	N	ASP	A	48	46.200	8.931	67.703	1.00	46.81
ATOM	392	CA	ASP	A	48	45.918	9.062	66.275	1.00	46.76

ATOM	393	C	ASP	A	48	45.454	7.728	65.664	1.00	43.75
ATOM	394	O	ASP	A	48	45.634	6.647	66.228	1.00	43.52
ATOM	395	CB	ASP	A	48	47.139	9.590	65.505	1.00	46.15
ATOM	396	CG	ASP	A	48	46.753	10.511	64.337	1.00	46.12
ATOM	397	OD1	ASP	A	48	45.610	10.448	63.865	1.00	47.80
ATOM	398	OD2	ASP	A	48	47.520	11.345	63.824	1.00	45.97
ATOM	399	N	VAL	A	49	44.837	7.855	64.503	1.00	39.86
ATOM	400	CA	VAL	A	49	44.386	6.746	63.695	1.00	40.09
ATOM	401	C	VAL	A	49	45.550	5.875	63.214	1.00	35.44
ATOM	402	O	VAL	A	49	46.690	6.335	63.105	1.00	34.85
ATOM	403	CB	VAL	A	49	43.565	7.342	62.512	1.00	45.24
ATOM	404	CG1	VAL	A	49	43.677	6.530	61.240	1.00	46.89
ATOM	405	CG2	VAL	A	49	42.111	7.550	62.942	1.00	44.64
ATOM	406	N	SER	A	50	45.270	4.599	62.963	1.00	30.48
ATOM	407	CA	SER	A	50	46.239	3.721	62.311	1.00	32.31
ATOM	408	C	SER	A	50	45.821	3.522	60.858	1.00	30.62
ATOM	409	O	SER	A	50	44.628	3.445	60.566	1.00	27.62
ATOM	410	CB	SER	A	50	46.301	2.353	63.001	1.00	36.08
ATOM	411	OG	SER	A	50	46.626	2.460	64.373	1.00	40.07
ATOM	412	N	PRO	A	51	46.788	3.414	59.950	1.00	28.51
ATOM	413	CA	PRO	A	51	46.485	3.159	58.547	1.00	28.46
ATOM	414	C	PRO	A	51	46.182	1.679	58.272	1.00	33.24
ATOM	415	O	PRO	A	51	46.963	0.814	58.738	1.00	31.33
ATOM	416	CB	PRO	A	51	47.784	3.521	57.852	1.00	24.78
ATOM	417	CG	PRO	A	51	48.813	3.248	58.844	1.00	26.09
ATOM	418	CD	PRO	A	51	48.238	3.489	60.180	1.00	26.48
ATOM	419	N	PHE	A	52	45.120	1.401	57.501	1.00	30.61
ATOM	420	CA	PHE	A	52	44.864	0.029	57.026	1.00	28.44
ATOM	421	C	PHE	A	52	46.004	-0.422	56.175	1.00	29.63
ATOM	422	O	PHE	A	52	46.594	0.370	55.429	1.00	32.01
ATOM	423	CB	PHE	A	52	43.626	-0.068	56.169	1.00	24.75
ATOM	424	CG	PHE	A	52	42.387	0.405	56.831	1.00	22.32
ATOM	425	CD1	PHE	A	52	42.085	0.040	58.124	1.00	23.62
ATOM	426	CD2	PHE	A	52	41.491	1.199	56.125	1.00	25.33
ATOM	427	CE1	PHE	A	52	40.904	0.463	58.713	1.00	23.34
ATOM	428	CE2	PHE	A	52	40.328	1.612	56.683	1.00	21.27
ATOM	429	CZ	PHE	A	52	40.024	1.254	57.986	1.00	28.10
ATOM	430	N	ASP	A	53	46.322	-1.704	56.279	1.00	28.69
ATOM	431	CA	ASP	A	53	47.356	-2.294	55.451	1.00	29.49
ATOM	432	C	ASP	A	53	47.130	-2.099	53.960	1.00	27.77
ATOM	433	O	ASP	A	53	48.064	-1.788	53.237	1.00	32.33
ATOM	434	CB	ASP	A	53	47.477	-3.792	55.743	1.00	35.42
ATOM	435	CG	ASP	A	53	48.004	-4.065	57.126	1.00	38.63
ATOM	436	OD1	ASP	A	53	48.904	-3.317	57.572	1.00	39.43
ATOM	437	OD2	ASP	A	53	47.570	-4.992	57.835	1.00	37.94
ATOM	438	N	HIS	A	54	45.905	-2.295	53.496	1.00	30.15
ATOM	439	CA	HIS	A	54	45.671	-2.394	52.057	1.00	32.40
ATOM	440	C	HIS	A	54	45.927	-1.071	51.339	1.00	34.34
ATOM	441	O	HIS	A	54	46.338	-1.063	50.174	1.00	32.57
ATOM	442	CB	HIS	A	54	44.253	-2.920	51.757	1.00	30.82
ATOM	443	CG	HIS	A	54	43.144	-1.926	51.968	1.00	31.84
ATOM	444	ND1	HIS	A	54	42.695	-1.081	50.973	1.00	31.38
ATOM	445	CD2	HIS	A	54	42.342	-1.700	53.032	1.00	29.25
ATOM	446	CE1	HIS	A	54	41.682	-0.367	51.423	1.00	25.81
ATOM	447	NE2	HIS	A	54	41.450	-0.718	52.673	1.00	28.42
ATOM	448	N	SER	A	55	45.691	0.034	52.052	1.00	33.04
ATOM	449	CA	SER	A	55	45.764	1.360	51.463	1.00	31.70
ATOM	450	C	SER	A	55	46.975	2.163	51.953	1.00	32.19

ATOM	451	O	SER	A	55	47.131	3.315	51.575	1.00	31.89
ATOM	452	CB	SER	A	55	44.472	2.125	51.740	1.00	27.88
ATOM	453	OG	SER	A	55	44.171	2.174	53.135	1.00	29.64
ATOM	454	N	ARG	A	56	47.846	1.564	52.758	1.00	29.31
ATOM	455	CA	ARG	A	56	48.968	2.309	53.310	1.00	28.34
ATOM	456	C	ARG	A	56	49.965	2.696	52.244	1.00	30.31
ATOM	457	O	ARG	A	56	50.159	1.980	51.272	1.00	32.53
ATOM	458	CB	ARG	A	56	49.653	1.555	54.452	1.00	29.43
ATOM	459	CG	ARG	A	56	50.655	0.459	54.047	1.00	29.42
ATOM	460	CD	ARG	A	56	51.106	-0.405	55.255	1.00	31.42
ATOM	461	NE	ARG	A	56	52.173	-1.315	54.865	1.00	32.84
ATOM	462	CZ	ARG	A	56	53.458	-1.039	54.853	1.00	35.87
ATOM	463	NH1	ARG	A	56	53.933	0.127	55.264	1.00	39.34
ATOM	464	NH2	ARG	A	56	54.296	-1.972	54.431	1.00	39.78
ATOM	465	N	ILE	A	57	50.582	3.860	52.430	1.00	33.20
ATOM	466	CA	ILE	A	57	51.638	4.334	51.552	1.00	32.52
ATOM	467	C	ILE	A	57	52.938	3.718	52.035	1.00	33.53
ATOM	468	O	ILE	A	57	53.244	3.740	53.230	1.00	33.31
ATOM	469	CB	ILE	A	57	51.767	5.902	51.604	1.00	32.19
ATOM	470	CG1	ILE	A	57	50.527	6.591	51.022	1.00	29.83
ATOM	471	CG2	ILE	A	57	53.014	6.365	50.887	1.00	27.84
ATOM	472	CD1	ILE	A	57	50.344	6.439	49.507	1.00	28.71
ATOM	473	N	LYS	A	58	53.718	3.200	51.103	1.00	33.28
ATOM	474	CA	LYS	A	58	54.993	2.598	51.439	1.00	35.42
ATOM	475	C	LYS	A	58	56.109	3.545	51.072	1.00	33.07
ATOM	476	O	LYS	A	58	56.159	4.072	49.958	1.00	33.66
ATOM	477	CB	LYS	A	58	55.170	1.264	50.708	1.00	39.50
ATOM	478	CG	LYS	A	58	54.212	0.177	51.179	1.00	41.43
ATOM	479	CD	LYS	A	58	54.570	-1.156	50.547	1.00	47.70
ATOM	480	CE	LYS	A	58	53.434	-2.167	50.648	1.00	49.64
ATOM	481	NZ	LYS	A	58	53.870	-3.471	50.068	1.00	53.45
ATOM	482	N	LEU	A	59	56.983	3.794	52.039	1.00	29.97
ATOM	483	CA	LEU	A	59	58.233	4.473	51.773	1.00	34.56
ATOM	484	C	LEU	A	59	59.072	3.533	50.916	1.00	36.28
ATOM	485	O	LEU	A	59	58.980	2.325	51.075	1.00	37.81
ATOM	486	CB	LEU	A	59	58.942	4.833	53.091	1.00	32.21
ATOM	487	CG	LEU	A	59	58.153	5.722	54.071	1.00	29.92
ATOM	488	CD1	LEU	A	59	58.894	5.903	55.399	1.00	32.91
ATOM	489	CD2	LEU	A	59	57.875	7.066	53.428	1.00	27.92
ATOM	490	N	HIS	A	60	59.853	4.090	49.991	1.00	41.69
ATOM	491	CA	HIS	A	60	60.690	3.310	49.084	1.00	45.51
ATOM	492	C	HIS	A	60	62.100	3.252	49.671	1.00	50.69
ATOM	493	O	HIS	A	60	63.052	3.731	49.062	1.00	55.71
ATOM	494	CB	HIS	A	60	60.738	3.935	47.670	1.00	46.25
ATOM	495	CG	HIS	A	60	59.400	4.042	46.996	1.00	47.90
ATOM	496	ND1	HIS	A	60	59.099	5.043	46.097	1.00	48.42
ATOM	497	CD2	HIS	A	60	58.286	3.277	47.089	1.00	51.06
ATOM	498	CE1	HIS	A	60	57.859	4.892	45.667	1.00	45.41
ATOM	499	NE2	HIS	A	60	57.341	3.832	46.257	1.00	49.77
ATOM	500	N	GLN	A	61	62.217	2.721	50.880	1.00	55.19
ATOM	501	CA	GLN	A	61	63.515	2.435	51.486	1.00	61.19
ATOM	502	C	GLN	A	61	63.514	0.957	51.874	1.00	64.61
ATOM	503	O	GLN	A	61	62.447	0.359	52.077	1.00	64.15
ATOM	504	CB	GLN	A	61	63.813	3.359	52.689	1.00	62.20
ATOM	505	CG	GLN	A	61	62.705	3.478	53.743	1.00	63.36
ATOM	506	CD	GLN	A	61	63.115	4.319	54.981	1.00	66.07
ATOM	507	OE1	GLN	A	61	63.334	3.767	56.069	1.00	68.99
ATOM	508	NE2	GLN	A	61	63.193	5.642	54.817	1.00	57.39

ATOM	509	N	GLU	A	62	64.698	0.358	51.931	1.00	68.33
ATOM	510	CA	GLU	A	62	64.806	-1.077	52.212	1.00	71.80
ATOM	511	C	GLU	A	62	64.616	-1.382	53.702	1.00	71.23
ATOM	512	O	GLU	A	62	64.096	-2.438	54.066	1.00	71.32
ATOM	513	CB	GLU	A	62	66.152	-1.627	51.712	1.00	74.26
ATOM	514	CG	GLU	A	62	66.105	-2.165	50.282	1.00	78.26
ATOM	515	CD	GLU	A	62	67.440	-2.074	49.551	1.00	81.64
ATOM	516	OE1	GLU	A	62	68.503	-1.974	50.214	1.00	81.39
ATOM	517	OE2	GLU	A	62	67.424	-2.107	48.298	1.00	84.40
ATOM	518	N	ASP	A	63	65.010	-0.435	54.551	1.00	71.07
ATOM	519	CA	ASP	A	63	65.050	-0.633	56.002	1.00	70.34
ATOM	520	C	ASP	A	63	63.651	-0.881	56.598	1.00	65.10
ATOM	521	O	ASP	A	63	63.319	-2.008	56.975	1.00	65.91
ATOM	522	CB	ASP	A	63	65.750	0.572	56.670	1.00	73.08
ATOM	523	CG	ASP	A	63	66.320	0.243	58.042	1.00	77.45
ATOM	524	OD1	ASP	A	63	67.352	-0.468	58.109	1.00	79.35
ATOM	525	OD2	ASP	A	63	65.813	0.668	59.107	1.00	80.87
ATOM	526	N	ASN	A	64	62.844	0.174	56.675	1.00	58.43
ATOM	527	CA	ASN	A	64	61.477	0.099	57.193	1.00	52.04
ATOM	528	C	ASN	A	64	60.627	1.023	56.332	1.00	48.60
ATOM	529	O	ASN	A	64	60.852	2.233	56.303	1.00	47.24
ATOM	530	CB	ASN	A	64	61.413	0.522	58.668	1.00	48.57
ATOM	531	CG	ASN	A	64	60.047	0.296	59.277	1.00	49.39
ATOM	532	OD1	ASN	A	64	59.097	-0.023	58.567	1.00	52.11
ATOM	533	ND2	ASN	A	64	59.934	0.459	60.597	1.00	43.17
ATOM	534	N	ASP	A	65	59.671	0.447	55.614	1.00	44.68
ATOM	535	CA	ASP	A	65	58.893	1.200	54.640	1.00	41.56
ATOM	536	C	ASP	A	65	57.637	1.859	55.230	1.00	37.75
ATOM	537	O	ASP	A	65	56.816	2.386	54.488	1.00	37.27
ATOM	538	CB	ASP	A	65	58.546	0.312	53.424	1.00	42.30
ATOM	539	CG	ASP	A	65	57.516	-0.766	53.730	1.00	41.84
ATOM	540	OD1	ASP	A	65	56.979	-0.819	54.847	1.00	42.12
ATOM	541	OD2	ASP	A	65	57.175	-1.614	52.887	1.00	47.21
ATOM	542	N	TYR	A	66	57.495	1.836	56.553	1.00	32.69
ATOM	543	CA	TYR	A	66	56.263	2.258	57.185	1.00	34.98
ATOM	544	C	TYR	A	66	56.171	3.765	57.523	1.00	30.91
ATOM	545	O	TYR	A	66	57.059	4.359	58.106	1.00	30.40
ATOM	546	CB	TYR	A	66	55.983	1.446	58.443	1.00	29.07
ATOM	547	CG	TYR	A	66	54.739	1.934	59.146	1.00	31.86
ATOM	548	CD1	TYR	A	66	53.481	1.556	58.712	1.00	29.85
ATOM	549	CD2	TYR	A	66	54.821	2.799	60.228	1.00	31.65
ATOM	550	CE1	TYR	A	66	52.339	2.006	59.347	1.00	27.49
ATOM	551	CE2	TYR	A	66	53.682	3.257	60.874	1.00	30.06
ATOM	552	CZ	TYR	A	66	52.442	2.867	60.426	1.00	27.92
ATOM	553	OH	TYR	A	66	51.298	3.317	61.057	1.00	23.79
ATOM	554	N	ILE	A	67	55.041	4.342	57.148	1.00	31.87
ATOM	555	CA	ILE	A	67	54.637	5.669	57.594	1.00	28.25
ATOM	556	C	ILE	A	67	53.140	5.603	57.818	1.00	26.62
ATOM	557	O	ILE	A	67	52.426	4.932	57.063	1.00	27.32
ATOM	558	CB	ILE	A	67	55.010	6.737	56.519	1.00	26.62
ATOM	559	CG1	ILE	A	67	54.582	8.146	56.964	1.00	25.26
ATOM	560	CG2	ILE	A	67	54.383	6.378	55.166	1.00	27.78
ATOM	561	CD1	ILE	A	67	55.183	9.282	56.135	1.00	23.21
ATOM	562	N	ASN	A	68	52.663	6.274	58.856	1.00	24.43
ATOM	563	CA	ASN	A	68	51.248	6.399	59.090	1.00	26.84
ATOM	564	C	ASN	A	68	50.614	7.339	58.044	1.00	29.79
ATOM	565	O	ASN	A	68	50.396	8.529	58.301	1.00	27.07
ATOM	566	CB	ASN	A	68	50.966	6.891	60.504	1.00	23.80

ATOM	567	CG	ASN	A	68	49.514	6.815	60.844	1.00	27.62
ATOM	568	OD1	ASN	A	68	48.672	6.723	59.950	1.00	33.26
ATOM	569	ND2	ASN	A	68	49.190	6.842	62.127	1.00	29.87
ATOM	570	N	ALA	A	69	50.335	6.776	56.869	1.00	26.62
ATOM	571	CA	ALA	A	69	49.661	7.473	55.785	1.00	26.37
ATOM	572	C	ALA	A	69	48.863	6.476	54.931	1.00	28.38
ATOM	573	O	ALA	A	69	49.277	5.316	54.764	1.00	25.53
ATOM	574	CB	ALA	A	69	50.660	8.224	54.934	1.00	25.04
ATOM	575	N	SER	A	70	47.728	6.943	54.403	1.00	26.26
ATOM	576	CA	SER	A	70	46.806	6.118	53.629	1.00	26.54
ATOM	577	C	SER	A	70	46.455	6.824	52.323	1.00	28.75
ATOM	578	O	SER	A	70	46.271	8.039	52.310	1.00	25.27
ATOM	579	CB	SER	A	70	45.511	5.891	54.401	1.00	23.26
ATOM	580	OG	SER	A	70	45.728	5.431	55.728	1.00	26.58
ATOM	581	N	LEU	A	71	46.347	6.052	51.246	1.00	26.40
ATOM	582	CA	LEU	A	71	45.835	6.527	49.969	1.00	26.16
ATOM	583	C	LEU	A	71	44.329	6.317	49.851	1.00	27.58
ATOM	584	O	LEU	A	71	43.828	5.190	49.930	1.00	31.42
ATOM	585	CB	LEU	A	71	46.564	5.863	48.817	1.00	27.02
ATOM	586	CG	LEU	A	71	46.149	6.190	47.374	1.00	27.68
ATOM	587	CD1	LEU	A	71	46.751	5.131	46.382	1.00	29.17
ATOM	588	CD2	LEU	A	71	46.580	7.597	46.956	1.00	30.23
ATOM	589	N	ILE	A	72	43.614	7.429	49.704	1.00	27.27
ATOM	590	CA	ILE	A	72	42.190	7.452	49.457	1.00	29.78
ATOM	591	C	ILE	A	72	42.054	7.655	47.948	1.00	33.13
ATOM	592	O	ILE	A	72	42.507	8.664	47.413	1.00	29.74
ATOM	593	CB	ILE	A	72	41.530	8.616	50.182	1.00	29.24
ATOM	594	CG1	ILE	A	72	41.497	8.436	51.698	1.00	33.27
ATOM	595	CG2	ILE	A	72	40.098	8.791	49.713	1.00	31.42
ATOM	596	CD1	ILE	A	72	42.801	8.343	52.352	1.00	39.18
ATOM	597	N	LYS	A	73	41.459	6.690	47.262	1.00	31.14
ATOM	598	CA	LYS	A	73	41.370	6.744	45.810	1.00	35.01
ATOM	599	C	LYS	A	73	39.910	6.820	45.454	1.00	31.26
ATOM	600	O	LYS	A	73	39.156	5.874	45.708	1.00	32.26
ATOM	601	CB	LYS	A	73	42.032	5.526	45.175	1.00	38.92
ATOM	602	CG	LYS	A	73	42.707	5.838	43.842	1.00	49.66
ATOM	603	CD	LYS	A	73	43.222	4.576	43.129	1.00	56.02
ATOM	604	CE	LYS	A	73	44.527	4.066	43.749	1.00	59.01
ATOM	605	NZ	LYS	A	73	44.757	2.611	43.510	1.00	62.37
ATOM	606	N	MET	A	74	39.481	7.966	44.934	1.00	26.18
ATOM	607	CA	MET	A	74	38.069	8.129	44.575	1.00	27.64
ATOM	608	C	MET	A	74	37.944	7.987	43.069	1.00	29.42
ATOM	609	O	MET	A	74	38.197	8.931	42.309	1.00	30.17
ATOM	610	CB	MET	A	74	37.512	9.441	45.096	1.00	27.81
ATOM	611	CG	MET	A	74	37.712	9.614	46.593	1.00	30.72
ATOM	612	SD	MET	A	74	36.826	8.410	47.617	1.00	31.58
ATOM	613	CE	MET	A	74	35.155	8.853	47.354	1.00	27.53
ATOM	614	N	GLU	A	75	37.611	6.764	42.651	1.00	32.89
ATOM	615	CA	GLU	A	75	37.606	6.352	41.238	1.00	35.37
ATOM	616	C	GLU	A	75	36.704	7.213	40.343	1.00	27.34
ATOM	617	O	GLU	A	75	37.151	7.727	39.330	1.00	31.16
ATOM	618	CB	GLU	A	75	37.191	4.867	41.129	1.00	40.62
ATOM	619	CG	GLU	A	75	37.470	4.231	39.774	1.00	48.74
ATOM	620	CD	GLU	A	75	37.322	2.715	39.787	1.00	54.93
ATOM	621	OE1	GLU	A	75	36.174	2.224	39.768	1.00	60.04
ATOM	622	OE2	GLU	A	75	38.357	2.008	39.815	1.00	63.82
ATOM	623	N	GLU	A	76	35.440	7.362	40.711	1.00	28.64
ATOM	624	CA	GLU	A	76	34.497	8.117	39.893	1.00	29.79

ATOM	625	C	GLU	A	76	34.881	9.603	39.808	1.00	33.33
ATOM	626	O	GLU	A	76	34.785	10.206	38.742	1.00	31.81
ATOM	627	CB	GLU	A	76	33.079	7.998	40.443	1.00	31.29
ATOM	628	CG	GLU	A	76	32.031	8.574	39.505	1.00	32.55
ATOM	629	CD	GLU	A	76	30.689	8.782	40.159	1.00	33.85
ATOM	630	OE1	GLU	A	76	30.479	8.342	41.316	1.00	32.93
ATOM	631	OE2	GLU	A	76	29.838	9.410	39.502	1.00	37.55
ATOM	632	N	ALA	A	77	35.311	10.187	40.931	1.00	31.97
ATOM	633	CA	ALA	A	77	35.668	11.599	40.964	1.00	28.17
ATOM	634	C	ALA	A	77	37.032	11.856	40.349	1.00	26.78
ATOM	635	O	ALA	A	77	37.390	12.990	40.085	1.00	31.00
ATOM	636	CB	ALA	A	77	35.627	12.113	42.400	1.00	29.56
ATOM	637	N	GLN	A	78	37.803	10.793	40.137	1.00	27.94
ATOM	638	CA	GLN	A	78	39.180	10.886	39.667	1.00	29.55
ATOM	639	C	GLN	A	78	40.055	11.791	40.550	1.00	28.24
ATOM	640	O	GLN	A	78	40.840	12.595	40.066	1.00	29.87
ATOM	641	CB	GLN	A	78	39.232	11.263	38.167	1.00	36.39
ATOM	642	CG	GLN	A	78	38.797	10.096	37.229	1.00	40.91
ATOM	643	CD	GLN	A	78	39.758	8.891	37.277	1.00	44.12
ATOM	644	OE1	GLN	A	78	40.866	8.955	36.741	1.00	45.28
ATOM	645	NE2	GLN	A	78	39.333	7.805	37.926	1.00	44.61
ATOM	646	N	ARG	A	79	39.940	11.604	41.859	1.00	26.27
ATOM	647	CA	ARG	A	79	40.784	12.298	42.834	1.00	27.36
ATOM	648	C	ARG	A	79	41.427	11.294	43.735	1.00	27.37
ATOM	649	O	ARG	A	79	40.787	10.349	44.172	1.00	25.21
ATOM	650	CB	ARG	A	79	39.953	13.206	43.734	1.00	25.02
ATOM	651	CG	ARG	A	79	39.619	14.494	43.106	1.00	27.59
ATOM	652	CD	ARG	A	79	40.706	15.532	43.201	1.00	24.51
ATOM	653	NE	ARG	A	79	40.107	16.836	43.414	1.00	29.17
ATOM	654	CZ	ARG	A	79	40.020	17.805	42.517	1.00	27.84
ATOM	655	NH1	ARG	A	79	39.449	18.944	42.876	1.00	30.27
ATOM	656	NH2	ARG	A	79	40.478	17.662	41.284	1.00	27.06
ATOM	657	N	SER	A	80	42.686	11.547	44.056	1.00	24.62
ATOM	658	CA	SER	A	80	43.380	10.826	45.086	1.00	26.77
ATOM	659	C	SER	A	80	43.861	11.806	46.151	1.00	26.33
ATOM	660	O	SER	A	80	44.269	12.931	45.837	1.00	24.64
ATOM	661	CB	SER	A	80	44.560	10.082	44.471	1.00	28.33
ATOM	662	OG	SER	A	80	44.095	9.006	43.697	1.00	33.53
ATOM	663	N	TYR	A	81	43.821	11.361	47.405	1.00	24.21
ATOM	664	CA	TYR	A	81	44.408	12.085	48.531	1.00	23.65
ATOM	665	C	TYR	A	81	45.216	11.094	49.387	1.00	24.13
ATOM	666	O	TYR	A	81	44.814	9.938	49.555	1.00	24.40
ATOM	667	CB	TYR	A	81	43.311	12.713	49.401	1.00	22.88
ATOM	668	CG	TYR	A	81	42.102	13.270	48.670	1.00	23.10
ATOM	669	CD1	TYR	A	81	41.044	12.452	48.286	1.00	23.35
ATOM	670	CD2	TYR	A	81	42.000	14.630	48.390	1.00	21.42
ATOM	671	CE1	TYR	A	81	39.916	12.980	47.623	1.00	18.91
ATOM	672	CE2	TYR	A	81	40.887	15.156	47.741	1.00	22.29
ATOM	673	CZ	TYR	A	81	39.854	14.320	47.353	1.00	21.87
ATOM	674	OH	TYR	A	81	38.757	14.845	46.716	1.00	20.42
ATOM	675	N	ILE	A	82	46.355	11.532	49.916	1.00	20.24
ATOM	676	CA	ILE	A	82	47.060	10.802	50.963	1.00	20.61
ATOM	677	C	ILE	A	82	46.759	11.527	52.265	1.00	24.67
ATOM	678	O	ILE	A	82	47.032	12.728	52.355	1.00	24.93
ATOM	679	CB	ILE	A	82	48.581	10.810	50.725	1.00	22.20
ATOM	680	CG1	ILE	A	82	48.965	9.944	49.529	1.00	23.16
ATOM	681	CG2	ILE	A	82	49.309	10.327	51.984	1.00	22.16
ATOM	682	CD1	ILE	A	82	50.328	10.228	49.001	1.00	23.55

ATOM	683	N	LEU	A	83	46.177	10.820	53.245	1.00	22.39
ATOM	684	CA	LEU	A	83	45.939	11.359	54.574	1.00	22.02
ATOM	685	C	LEU	A	83	46.951	10.755	55.513	1.00	23.73
ATOM	686	O	LEU	A	83	47.179	9.560	55.520	1.00	22.83
ATOM	687	CB	LEU	A	83	44.519	11.096	55.082	1.00	23.84
ATOM	688	CG	LEU	A	83	43.488	12.171	54.725	1.00	26.43
ATOM	689	CD1	LEU	A	83	43.340	12.273	53.201	1.00	29.89
ATOM	690	CD2	LEU	A	83	42.141	11.863	55.353	1.00	30.50
ATOM	691	N	THR	A	84	47.575	11.604	56.307	1.00	21.81
ATOM	692	CA	THR	A	84	48.629	11.163	57.189	1.00	21.57
ATOM	693	C	THR	A	84	48.499	11.897	58.510	1.00	22.44
ATOM	694	O	THR	A	84	47.605	12.757	58.680	1.00	20.53
ATOM	695	CB	THR	A	84	49.983	11.320	56.482	1.00	21.64
ATOM	696	OG1	THR	A	84	51.020	10.742	57.262	1.00	24.20
ATOM	697	CG2	THR	A	84	50.368	12.811	56.253	1.00	23.01
ATOM	698	N	GLN	A	85	49.285	11.453	59.488	1.00	22.81
ATOM	699	CA	GLN	A	85	49.354	12.121	60.780	1.00	23.95
ATOM	700	C	GLN	A	85	50.307	13.321	60.659	1.00	23.08
ATOM	701	O	GLN	A	85	51.226	13.346	59.798	1.00	23.89
ATOM	702	CB	GLN	A	85	49.860	11.149	61.874	1.00	21.50
ATOM	703	CG	GLN	A	85	51.301	10.780	61.733	1.00	22.55
ATOM	704	CD	GLN	A	85	51.762	9.690	62.700	1.00	25.69
ATOM	705	OE1	GLN	A	85	50.951	8.958	63.282	1.00	26.39
ATOM	706	NE2	GLN	A	85	53.072	9.580	62.858	1.00	23.52
ATOM	707	N	GLY	A	86	50.133	14.278	61.551	1.00	23.87
ATOM	708	CA	GLY	A	86	51.092	15.359	61.690	1.00	27.12
ATOM	709	C	GLY	A	86	52.425	14.728	62.032	1.00	24.81
ATOM	710	O	GLY	A	86	52.469	13.820	62.884	1.00	25.33
ATOM	711	N	PRO	A	87	53.482	15.108	61.317	1.00	23.19
ATOM	712	CA	PRO	A	87	54.812	14.559	61.561	1.00	25.56
ATOM	713	C	PRO	A	87	55.268	14.636	63.017	1.00	25.86
ATOM	714	O	PRO	A	87	54.982	15.603	63.721	1.00	23.39
ATOM	715	CB	PRO	A	87	55.703	15.417	60.673	1.00	27.59
ATOM	716	CG	PRO	A	87	54.831	15.854	59.576	1.00	25.39
ATOM	717	CD	PRO	A	87	53.468	15.982	60.131	1.00	25.14
ATOM	718	N	LEU	A	88	55.952	13.585	63.453	1.00	26.57
ATOM	719	CA	LEU	A	88	56.540	13.514	64.775	1.00	25.79
ATOM	720	C	LEU	A	88	57.967	14.044	64.697	1.00	27.23
ATOM	721	O	LEU	A	88	58.534	14.117	63.608	1.00	27.06
ATOM	722	CB	LEU	A	88	56.552	12.065	65.251	1.00	29.02
ATOM	723	CG	LEU	A	88	55.215	11.489	65.702	1.00	27.24
ATOM	724	CD1	LEU	A	88	54.878	11.952	67.109	1.00	23.82
ATOM	725	CD2	LEU	A	88	55.257	9.959	65.661	1.00	29.51
ATOM	726	N	PRO	A	89	58.563	14.397	65.837	1.00	26.76
ATOM	727	CA	PRO	A	89	59.963	14.848	65.859	1.00	28.66
ATOM	728	C	PRO	A	89	60.894	13.964	65.022	1.00	28.76
ATOM	729	O	PRO	A	89	61.788	14.484	64.331	1.00	30.30
ATOM	730	CB	PRO	A	89	60.324	14.796	67.346	1.00	27.52
ATOM	731	CG	PRO	A	89	59.040	15.032	68.049	1.00	26.96
ATOM	732	CD	PRO	A	89	57.969	14.400	67.185	1.00	28.31
ATOM	733	N	ASN	A	90	60.635	12.656	65.018	1.00	30.36
ATOM	734	CA	ASN	A	90	61.493	11.693	64.324	1.00	29.50
ATOM	735	C	ASN	A	90	60.937	11.167	63.000	1.00	28.62
ATOM	736	O	ASN	A	90	61.581	10.330	62.381	1.00	29.73
ATOM	737	CB	ASN	A	90	61.829	10.514	65.265	1.00	32.07
ATOM	738	CG	ASN	A	90	62.631	10.954	66.491	1.00	36.69
ATOM	739	OD1	ASN	A	90	63.659	11.634	66.364	1.00	37.94
ATOM	740	ND2	ASN	A	90	62.140	10.609	67.683	1.00	32.87

ATOM	741	N	THR	A	91	59.779	11.648	62.534	1.00	26.35
ATOM	742	CA	THR	A	91	59.263	11.209	61.223	1.00	25.63
ATOM	743	C	THR	A	91	59.124	12.313	60.193	1.00	26.37
ATOM	744	O	THR	A	91	58.444	12.134	59.194	1.00	25.56
ATOM	745	CB	THR	A	91	57.909	10.456	61.348	1.00	25.35
ATOM	746	OG1	THR	A	91	56.882	11.342	61.805	1.00	24.06
ATOM	747	CG2	THR	A	91	57.979	9.383	62.408	1.00	23.43
ATOM	748	N	CYS	A	92	59.770	13.451	60.420	1.00	25.07
ATOM	749	CA	CYS	A	92	59.765	14.538	59.439	1.00	25.34
ATOM	750	C	CYS	A	92	60.488	14.139	58.152	1.00	24.31
ATOM	751	O	CYS	A	92	60.055	14.490	57.043	1.00	23.94
ATOM	752	CB	CYS	A	92	60.410	15.802	60.039	1.00	27.99
ATOM	753	SG	CYS	A	92	59.459	16.529	61.381	1.00	24.33
ATOM	754	N	GLY	A	93	61.599	13.429	58.291	1.00	24.10
ATOM	755	CA	GLY	A	93	62.336	12.934	57.132	1.00	24.88
ATOM	756	C	GLY	A	93	61.498	11.989	56.288	1.00	28.13
ATOM	757	O	GLY	A	93	61.445	12.113	55.064	1.00	27.40
ATOM	758	N	HIS	A	94	60.812	11.075	56.978	1.00	28.43
ATOM	759	CA	HIS	A	94	59.881	10.133	56.372	1.00	28.20
ATOM	760	C	HIS	A	94	58.780	10.869	55.654	1.00	24.88
ATOM	761	O	HIS	A	94	58.410	10.517	54.542	1.00	22.84
ATOM	762	CB	HIS	A	94	59.216	9.248	57.443	1.00	28.80
ATOM	763	CG	HIS	A	94	60.172	8.458	58.275	1.00	29.78
ATOM	764	ND1	HIS	A	94	59.756	7.676	59.328	1.00	33.11
ATOM	765	CD2	HIS	A	94	61.518	8.321	58.213	1.00	34.96
ATOM	766	CE1	HIS	A	94	60.806	7.093	59.880	1.00	33.93
ATOM	767	NE2	HIS	A	94	61.887	7.470	59.225	1.00	29.90
ATOM	768	N	PHE	A	95	58.222	11.879	56.320	1.00	23.02
ATOM	769	CA	PHE	A	95	57.123	12.623	55.739	1.00	19.63
ATOM	770	C	PHE	A	95	57.539	13.220	54.399	1.00	21.27
ATOM	771	O	PHE	A	95	56.855	13.033	53.387	1.00	22.51
ATOM	772	CB	PHE	A	95	56.588	13.662	56.732	1.00	20.48
ATOM	773	CG	PHE	A	95	55.586	14.618	56.142	1.00	18.33
ATOM	774	CD1	PHE	A	95	54.233	14.401	56.299	1.00	20.98
ATOM	775	CD2	PHE	A	95	56.011	15.736	55.429	1.00	20.21
ATOM	776	CE1	PHE	A	95	53.305	15.278	55.771	1.00	25.19
ATOM	777	CE2	PHE	A	95	55.091	16.636	54.899	1.00	20.58
ATOM	778	CZ	PHE	A	95	53.732	16.408	55.073	1.00	25.85
ATOM	779	N	TRP	A	96	58.668	13.916	54.370	1.00	23.70
ATOM	780	CA	TRP	A	96	59.111	14.547	53.134	1.00	21.44
ATOM	781	C	TRP	A	96	59.583	13.514	52.113	1.00	26.85
ATOM	782	O	TRP	A	96	59.481	13.734	50.904	1.00	25.37
ATOM	783	CB	TRP	A	96	60.180	15.601	53.428	1.00	24.68
ATOM	784	CG	TRP	A	96	59.561	16.795	54.090	1.00	21.64
ATOM	785	CD1	TRP	A	96	59.737	17.221	55.376	1.00	21.49
ATOM	786	CD2	TRP	A	96	58.602	17.666	53.508	1.00	23.92
ATOM	787	NE1	TRP	A	96	58.955	18.327	55.616	1.00	26.29
ATOM	788	CE2	TRP	A	96	58.257	18.625	54.479	1.00	21.97
ATOM	789	CE3	TRP	A	96	58.012	17.754	52.237	1.00	25.15
ATOM	790	CZ2	TRP	A	96	57.353	19.630	54.230	1.00	23.22
ATOM	791	CZ3	TRP	A	96	57.112	18.749	51.996	1.00	20.27
ATOM	792	CH2	TRP	A	96	56.778	19.667	52.985	1.00	22.62
ATOM	793	N	GLU	A	97	60.038	12.365	52.588	1.00	30.30
ATOM	794	CA	GLU	A	97	60.350	11.246	51.698	1.00	31.44
ATOM	795	C	GLU	A	97	59.100	10.819	50.950	1.00	28.25
ATOM	796	O	GLU	A	97	59.127	10.632	49.745	1.00	26.11
ATOM	797	CB	GLU	A	97	60.900	10.031	52.459	1.00	32.06
ATOM	798	CG	GLU	A	97	61.199	8.868	51.521	1.00	31.62

ATOM	799	CD	GLU	A	97	61.797	7.647	52.196	1.00	33.54
ATOM	800	OE1	GLU	A	97	62.047	7.685	53.414	1.00	33.60
ATOM	801	OE2	GLU	A	97	62.002	6.630	51.490	1.00	33.83
ATOM	802	N	MET	A	98	58.009	10.654	51.680	1.00	28.99
ATOM	803	CA	MET	A	98	56.746	10.295	51.066	1.00	25.04
ATOM	804	C	MET	A	98	56.325	11.357	50.057	1.00	28.35
ATOM	805	O	MET	A	98	55.939	11.011	48.947	1.00	29.80
ATOM	806	CB	MET	A	98	55.678	10.092	52.123	1.00	22.99
ATOM	807	CG	MET	A	98	54.289	9.880	51.562	1.00	27.35
ATOM	808	SD	MET	A	98	53.081	9.519	52.796	1.00	26.88
ATOM	809	CE	MET	A	98	52.976	11.131	53.675	1.00	28.20
ATOM	810	N	VAL	A	99	56.394	12.641	50.422	1.00	27.18
ATOM	811	CA	VAL	A	99	56.030	13.718	49.486	1.00	25.66
ATOM	812	C	VAL	A	99	56.845	13.637	48.186	1.00	30.66
ATOM	813	O	VAL	A	99	56.286	13.772	47.091	1.00	28.50
ATOM	814	CB	VAL	A	99	56.212	15.108	50.100	1.00	25.29
ATOM	815	CG1	VAL	A	99	56.054	16.177	49.051	1.00	25.73
ATOM	816	CG2	VAL	A	99	55.207	15.348	51.238	1.00	24.18
ATOM	817	N	TRP	A	100	58.151	13.396	48.319	1.00	29.79
ATOM	818	CA	TRP	A	100	59.046	13.220	47.179	1.00	30.99
ATOM	819	C	TRP	A	100	58.619	12.052	46.269	1.00	30.01
ATOM	820	O	TRP	A	100	58.342	12.241	45.095	1.00	32.13
ATOM	821	CB	TRP	A	100	60.498	12.973	47.655	1.00	34.76
ATOM	822	CG	TRP	A	100	61.439	12.866	46.498	1.00	37.10
ATOM	823	CD1	TRP	A	100	61.774	11.730	45.802	1.00	40.72
ATOM	824	CD2	TRP	A	100	62.097	13.941	45.846	1.00	41.47
ATOM	825	NE1	TRP	A	100	62.620	12.044	44.766	1.00	36.22
ATOM	826	CE2	TRP	A	100	62.832	13.395	44.765	1.00	44.00
ATOM	827	CE3	TRP	A	100	62.144	15.323	46.057	1.00	41.72
ATOM	828	CZ2	TRP	A	100	63.608	14.184	43.912	1.00	45.14
ATOM	829	CZ3	TRP	A	100	62.919	16.101	45.218	1.00	45.12
ATOM	830	CH2	TRP	A	100	63.639	15.530	44.154	1.00	46.67
ATOM	831	N	GLU	A	101	58.559	10.858	46.841	1.00	29.76
ATOM	832	CA	GLU	A	101	58.296	9.623	46.109	1.00	31.91
ATOM	833	C	GLU	A	101	56.897	9.542	45.500	1.00	33.10
ATOM	834	O	GLU	A	101	56.717	8.953	44.436	1.00	31.24
ATOM	835	CB	GLU	A	101	58.513	8.428	47.042	1.00	33.49
ATOM	836	CG	GLU	A	101	59.986	8.235	47.416	1.00	35.52
ATOM	837	CD	GLU	A	101	60.198	7.324	48.613	1.00	36.36
ATOM	838	OE1	GLU	A	101	59.208	6.722	49.114	1.00	34.30
ATOM	839	OE2	GLU	A	101	61.372	7.210	49.045	1.00	33.40
ATOM	840	N	GLN	A	102	55.910	10.126	46.175	1.00	28.75
ATOM	841	CA	GLN	A	102	54.538	10.120	45.677	1.00	29.37
ATOM	842	C	GLN	A	102	54.295	11.220	44.663	1.00	28.29
ATOM	843	O	GLN	A	102	53.213	11.300	44.086	1.00	31.13
ATOM	844	CB	GLN	A	102	53.544	10.212	46.842	1.00	30.91
ATOM	845	CG	GLN	A	102	53.617	9.000	47.798	1.00	31.45
ATOM	846	CD	GLN	A	102	53.496	7.656	47.061	1.00	32.80
ATOM	847	OE1	GLN	A	102	52.626	7.504	46.214	1.00	31.63
ATOM	848	NE2	GLN	A	102	54.365	6.702	47.384	1.00	32.99
ATOM	849	N	LYS	A	103	55.299	12.076	44.466	1.00	30.72
ATOM	850	CA	LYS	A	103	55.263	13.155	43.475	1.00	32.47
ATOM	851	C	LYS	A	103	54.163	14.179	43.750	1.00	27.03
ATOM	852	O	LYS	A	103	53.636	14.823	42.850	1.00	25.82
ATOM	853	CB	LYS	A	103	55.192	12.578	42.045	1.00	36.98
ATOM	854	CG	LYS	A	103	56.481	11.826	41.653	1.00	41.87
ATOM	855	CD	LYS	A	103	56.364	11.121	40.298	1.00	49.14
ATOM	856	CE	LYS	A	103	57.734	10.605	39.815	1.00	51.95

ATOM	857	NZ	LYS	A	103	58.541	10.021	40.935	1.00 54.94
ATOM	858	N	SER	A	104	53.831	14.326	45.020	1.00 25.84
ATOM	859	CA	SER	A	104	52.865	15.318	45.453	1.00 25.52
ATOM	860	C	SER	A	104	53.319	16.754	45.131	1.00 25.82
ATOM	861	O	SER	A	104	54.497	17.102	45.208	1.00 26.75
ATOM	862	CB	SER	A	104	52.632	15.179	46.958	1.00 26.43
ATOM	863	OG	SER	A	104	52.328	13.840	47.299	1.00 30.28
ATOM	864	N	ARG	A	105	52.353	17.577	44.781	1.00 27.47
ATOM	865	CA	ARG	A	105	52.569	18.977	44.524	1.00 29.78
ATOM	866	C	ARG	A	105	52.226	19.799	45.771	1.00 27.49
ATOM	867	O	ARG	A	105	52.850	20.808	46.046	1.00 26.55
ATOM	868	CB	ARG	A	105	51.668	19.378	43.358	1.00 32.18
ATOM	869	CG	ARG	A	105	52.147	20.517	42.532	1.00 42.19
ATOM	870	CD	ARG	A	105	51.696	21.835	43.034	1.00 48.41
ATOM	871	NE	ARG	A	105	52.155	22.954	42.219	1.00 55.25
ATOM	872	CZ	ARG	A	105	53.418	23.361	42.124	1.00 59.03
ATOM	873	NH1	ARG	A	105	54.400	22.750	42.773	1.00 62.40
ATOM	874	NH2	ARG	A	105	53.695	24.420	41.378	1.00 62.61
ATOM	875	N	GLY	A	106	51.217	19.364	46.509	1.00 28.11
ATOM	876	CA	GLY	A	106	50.689	20.120	47.634	1.00 25.59
ATOM	877	C	GLY	A	106	50.640	19.324	48.925	1.00 22.98
ATOM	878	O	GLY	A	106	50.481	18.092	48.917	1.00 22.43
ATOM	879	N	VAL	A	107	50.776	20.044	50.035	1.00 21.47
ATOM	880	CA	VAL	A	107	50.560	19.526	51.380	1.00 17.55
ATOM	881	C	VAL	A	107	49.532	20.450	51.987	1.00 21.98
ATOM	882	O	VAL	A	107	49.667	21.681	51.883	1.00 21.61
ATOM	883	CB	VAL	A	107	51.864	19.550	52.205	1.00 19.48
ATOM	884	CG1	VAL	A	107	51.606	19.250	53.665	1.00 20.01
ATOM	885	CG2	VAL	A	107	52.867	18.578	51.632	1.00 19.65
ATOM	886	N	VAL	A	108	48.476	19.862	52.548	1.00 20.07
ATOM	887	CA	VAL	A	108	47.370	20.582	53.155	1.00 21.81
ATOM	888	C	VAL	A	108	47.395	20.313	54.658	1.00 23.26
ATOM	889	O	VAL	A	108	47.252	19.163	55.102	1.00 21.40
ATOM	890	CB	VAL	A	108	46.023	20.162	52.562	1.00 22.26
ATOM	891	CG1	VAL	A	108	44.880	20.866	53.269	1.00 26.46
ATOM	892	CG2	VAL	A	108	45.984	20.479	51.065	1.00 22.10
ATOM	893	N	MET	A	109	47.623	21.380	55.431	1.00 22.08
ATOM	894	CA	MET	A	109	47.732	21.306	56.881	1.00 22.68
ATOM	895	C	MET	A	109	46.526	21.981	57.504	1.00 21.07
ATOM	896	O	MET	A	109	46.304	23.171	57.312	1.00 23.17
ATOM	897	CB	MET	A	109	49.024	21.972	57.340	1.00 23.07
ATOM	898	CG	MET	A	109	49.233	22.019	58.858	1.00 22.88
ATOM	899	SD	MET	A	109	50.928	22.520	59.237	1.00 24.38
ATOM	900	CE	MET	A	109	50.925	22.587	61.036	1.00 27.77
ATOM	901	N	LEU	A	110	45.740	21.224	58.259	1.00 21.69
ATOM	902	CA	LEU	A	110	44.481	21.755	58.778	1.00 20.78
ATOM	903	C	LEU	A	110	44.515	22.017	60.269	1.00 21.23
ATOM	904	O	LEU	A	110	43.485	22.050	60.916	1.00 29.08
ATOM	905	CB	LEU	A	110	43.347	20.786	58.448	1.00 24.47
ATOM	906	CG	LEU	A	110	43.108	20.528	56.966	1.00 24.58
ATOM	907	CD1	LEU	A	110	42.139	19.388	56.762	1.00 24.62
ATOM	908	CD2	LEU	A	110	42.602	21.776	56.325	1.00 29.12
ATOM	909	N	ASN	A	111	45.707	22.205	60.809	1.00 24.23
ATOM	910	CA	ASN	A	111	45.887	22.492	62.221	1.00 25.10
ATOM	911	C	ASN	A	111	47.004	23.514	62.423	1.00 23.03
ATOM	912	O	ASN	A	111	47.825	23.738	61.553	1.00 23.77
ATOM	913	CB	ASN	A	111	46.232	21.200	62.977	1.00 24.84
ATOM	914	CG	ASN	A	111	47.540	20.620	62.544	1.00 24.46

ATOM	915	OD1	ASN	A	111	47.638	20.087	61.457	1.00 24.90
ATOM	916	ND2	ASN	A	111	48.577	20.764	63.371	1.00 23.98
ATOM	917	N	ARG	A	112	47.025	24.109	63.601	1.00 24.79
ATOM	918	CA	ARG	A	112	48.175	24.832	64.074	1.00 22.03
ATOM	919	C	ARG	A	112	49.122	23.888	64.775	1.00 23.38
ATOM	920	O	ARG	A	112	48.713	22.857	65.340	1.00 21.21
ATOM	921	CB	ARG	A	112	47.736	25.940	65.023	1.00 26.48
ATOM	922	CG	ARG	A	112	47.170	27.143	64.305	1.00 27.70
ATOM	923	CD	ARG	A	112	46.483	28.152	65.225	1.00 32.52
ATOM	924	NE	ARG	A	112	45.281	27.582	65.821	1.00 35.60
ATOM	925	CZ	ARG	A	112	45.009	27.531	67.128	1.00 43.32
ATOM	926	NH1	ARG	A	112	45.823	28.057	68.050	1.00 46.30
ATOM	927	NH2	ARG	A	112	43.873	26.965	67.523	1.00 47.45
ATOM	928	N	VAL	A	113	50.396	24.256	64.745	1.00 25.41
ATOM	929	CA	VAL	A	113	51.439	23.532	65.433	1.00 26.91
ATOM	930	C	VAL	A	113	51.116	23.437	66.921	1.00 27.74
ATOM	931	O	VAL	A	113	51.286	22.379	67.532	1.00 25.36
ATOM	932	CB	VAL	A	113	52.804	24.185	65.182	1.00 29.50
ATOM	933	CG1	VAL	A	113	53.875	23.615	66.110	1.00 26.54
ATOM	934	CG2	VAL	A	113	53.201	23.978	63.717	1.00 30.55
ATOM	935	N	MET	A	114	50.585	24.520	67.475	1.00 26.52
ATOM	936	CA	MET	A	114	50.077	24.510	68.842	1.00 27.11
ATOM	937	C	MET	A	114	48.601	24.775	68.849	1.00 23.26
ATOM	938	O	MET	A	114	48.158	25.780	68.294	1.00 24.63
ATOM	939	CB	MET	A	114	50.757	25.584	69.708	1.00 26.78
ATOM	940	CG	MET	A	114	50.258	25.541	71.159	1.00 28.56
ATOM	941	SD	MET	A	114	51.448	26.265	72.371	1.00 31.45
ATOM	942	CE	MET	A	114	52.537	24.917	72.614	1.00 33.42
ATOM	943	N	GLU	A	115	47.841	23.879	69.485	1.00 22.46
ATOM	944	CA	GLU	A	115	46.419	24.094	69.734	1.00 24.62
ATOM	945	C	GLU	A	115	46.117	23.653	71.138	1.00 23.07
ATOM	946	O	GLU	A	115	46.683	22.674	71.597	1.00 23.93
ATOM	947	CB	GLU	A	115	45.570	23.238	68.757	1.00 27.38
ATOM	948	CG	GLU	A	115	45.668	23.711	67.323	1.00 30.60
ATOM	949	CD	GLU	A	115	44.909	22.854	66.330	1.00 30.65
ATOM	950	OE1	GLU	A	115	44.586	21.681	66.612	1.00 31.07
ATOM	951	OE2	GLU	A	115	44.672	23.377	65.242	1.00 28.57
ATOM	952	N	LYS	A	116	45.218	24.347	71.824	1.00 27.40
ATOM	953	CA	LYS	A	116	44.861	23.978	73.204	1.00 29.17
ATOM	954	C	LYS	A	116	46.099	23.920	74.107	1.00 26.13
ATOM	955	O	LYS	A	116	46.189	23.078	75.015	1.00 30.38
ATOM	956	CB	LYS	A	116	44.120	22.629	73.250	1.00 29.07
ATOM	957	CG	LYS	A	116	42.741	22.624	72.571	1.00 37.49
ATOM	958	CD	LYS	A	116	42.321	21.181	72.213	1.00 43.81
ATOM	959	CE	LYS	A	116	40.821	20.938	72.347	1.00 48.07
ATOM	960	NZ	LYS	A	116	40.464	19.530	71.998	1.00 49.95
ATOM	961	N	GLY	A	117	47.067	24.788	73.835	1.00 26.78
ATOM	962	CA	GLY	A	117	48.298	24.847	74.625	1.00 28.90
ATOM	963	C	GLY	A	117	49.222	23.641	74.523	1.00 27.34
ATOM	964	O	GLY	A	117	50.115	23.452	75.353	1.00 27.25
ATOM	965	N	SER	A	118	49.035	22.834	73.489	1.00 23.86
ATOM	966	CA	SER	A	118	49.773	21.587	73.355	1.00 26.52
ATOM	967	C	SER	A	118	50.291	21.438	71.917	1.00 24.21
ATOM	968	O	SER	A	118	49.675	21.899	70.973	1.00 24.79
ATOM	969	CB	SER	A	118	48.856	20.424	73.750	1.00 27.56
ATOM	970	OG	SER	A	118	49.518	19.184	73.637	1.00 40.87
ATOM	971	N	LEU	A	119	51.444	20.817	71.760	1.00 26.60
ATOM	972	CA	LEU	A	119	52.003	20.587	70.438	1.00 26.38

ATOM	973	C	LEU	A	119	51.266	19.490	69.683	1.00 27.04
ATOM	974	O	LEU	A	119	51.092	18.388	70.184	1.00 27.29
ATOM	975	CB	LEU	A	119	53.488	20.261	70.544	1.00 25.60
ATOM	976	CG	LEU	A	119	54.357	21.413	71.084	1.00 31.75
ATOM	977	CD1	LEU	A	119	55.806	20.985	71.131	1.00 34.60
ATOM	978	CD2	LEU	A	119	54.215	22.704	70.274	1.00 32.35
ATOM	979	N	LYS	A	120	50.856	19.806	68.456	1.00 24.78
ATOM	980	CA	LYS	A	120	50.049	18.922	67.638	1.00 28.04
ATOM	981	C	LYS	A	120	50.870	18.254	66.542	1.00 27.21
ATOM	982	O	LYS	A	120	50.482	17.214	66.037	1.00 30.85
ATOM	983	CB	LYS	A	120	48.868	19.698	67.043	1.00 27.25
ATOM	984	CG	LYS	A	120	47.934	20.246	68.108	1.00 30.57
ATOM	985	CD	LYS	A	120	47.238	19.108	68.911	1.00 33.63
ATOM	986	CE	LYS	A	120	46.840	19.569	70.300	1.00 33.92
ATOM	987	NZ	LYS	A	120	46.227	18.461	71.090	1.00 32.12
ATOM	988	N	CYS	A	121	51.982	18.873	66.170	1.00 28.54
ATOM	989	CA	CYS	A	121	52.980	18.258	65.309	1.00 29.45
ATOM	990	C	CYS	A	121	54.322	18.956	65.421	1.00 24.55
ATOM	991	O	CYS	A	121	54.432	20.038	66.003	1.00 26.49
ATOM	992	CB	CYS	A	121	52.536	18.229	63.829	1.00 33.36
ATOM	993	SG	CYS	A	121	52.300	19.820	63.026	1.00 31.09
ATOM	994	N	ALA	A	122	55.341	18.312	64.866	1.00 24.17
ATOM	995	CA	ALA	A	122	56.663	18.898	64.777	1.00 25.15
ATOM	996	C	ALA	A	122	56.625	20.091	63.815	1.00 24.39
ATOM	997	O	ALA	A	122	55.740	20.189	62.952	1.00 21.50
ATOM	998	CB	ALA	A	122	57.656	17.869	64.326	1.00 24.68
ATOM	999	N	GLN	A	123	57.534	21.041	64.024	1.00 30.52
ATOM	1000	CA	GLN	A	123	57.748	22.139	63.077	1.00 26.76
ATOM	1001	C	GLN	A	123	58.493	21.514	61.920	1.00 27.16
ATOM	1002	O	GLN	A	123	59.722	21.496	61.900	1.00 26.04
ATOM	1003	CB	GLN	A	123	58.555	23.275	63.738	1.00 30.31
ATOM	1004	CG	GLN	A	123	58.749	24.529	62.865	1.00 26.95
ATOM	1005	CD	GLN	A	123	57.434	25.088	62.373	1.00 25.90
ATOM	1006	OE1	GLN	A	123	56.534	25.382	63.178	1.00 28.50
ATOM	1007	NE2	GLN	A	123	57.294	25.203	61.052	1.00 19.25
ATOM	1008	N	TYR	A	124	57.745	20.969	60.955	1.00 26.91
ATOM	1009	CA	TYR	A	124	58.350	20.112	59.933	1.00 23.80
ATOM	1010	C	TYR	A	124	58.804	20.845	58.663	1.00 22.10
ATOM	1011	O	TYR	A	124	59.398	20.234	57.781	1.00 21.86
ATOM	1012	CB	TYR	A	124	57.425	18.921	59.611	1.00 22.76
ATOM	1013	CG	TYR	A	124	56.099	19.261	58.983	1.00 17.20
ATOM	1014	CD1	TYR	A	124	55.971	19.316	57.598	1.00 20.74
ATOM	1015	CD2	TYR	A	124	54.974	19.499	59.753	1.00 18.39
ATOM	1016	CE1	TYR	A	124	54.752	19.606	56.989	1.00 17.90
ATOM	1017	CE2	TYR	A	124	53.752	19.822	59.154	1.00 19.29
ATOM	1018	CZ	TYR	A	124	53.649	19.841	57.756	1.00 17.31
ATOM	1019	OH	TYR	A	124	52.464	20.152	57.113	1.00 16.79
ATOM	1020	N	TRP	A	125	58.540	22.147	58.593	1.00 25.93
ATOM	1021	CA	TRP	A	125	58.997	22.995	57.496	1.00 23.88
ATOM	1022	C	TRP	A	125	59.736	24.240	58.052	1.00 27.60
ATOM	1023	O	TRP	A	125	59.483	24.677	59.195	1.00 26.13
ATOM	1024	CB	TRP	A	125	57.808	23.402	56.617	1.00 22.08
ATOM	1025	CG	TRP	A	125	56.944	24.458	57.214	1.00 25.66
ATOM	1026	CD1	TRP	A	125	57.013	25.801	56.973	1.00 26.72
ATOM	1027	CD2	TRP	A	125	55.880	24.280	58.152	1.00 26.67
ATOM	1028	NE1	TRP	A	125	56.085	26.468	57.727	1.00 22.95
ATOM	1029	CE2	TRP	A	125	55.366	25.562	58.453	1.00 24.22
ATOM	1030	CE3	TRP	A	125	55.315	23.167	58.785	1.00 23.11

ATOM	1031	CZ2	TRP	A	125	54.314	25.760	59.347	1.00	25.50
ATOM	1032	CZ3	TRP	A	125	54.280	23.367	59.677	1.00	24.70
ATOM	1033	CH2	TRP	A	125	53.783	24.646	59.945	1.00	26.16
ATOM	1034	N	PRO	A	126	60.658	24.804	57.273	1.00	27.12
ATOM	1035	CA	PRO	A	126	61.423	25.971	57.737	1.00	28.25
ATOM	1036	C	PRO	A	126	60.554	27.216	57.804	1.00	24.48
ATOM	1037	O	PRO	A	126	59.742	27.466	56.922	1.00	28.44
ATOM	1038	CB	PRO	A	126	62.544	26.097	56.704	1.00	30.18
ATOM	1039	CG	PRO	A	126	62.052	25.416	55.499	1.00	31.77
ATOM	1040	CD	PRO	A	126	61.074	24.373	55.933	1.00	28.76
ATOM	1041	N	GLN	A	127	60.709	27.968	58.878	1.00	27.22
ATOM	1042	CA	GLN	A	127	59.988	29.207	59.082	1.00	30.34
ATOM	1043	C	GLN	A	127	60.672	30.438	58.437	1.00	31.05
ATOM	1044	O	GLN	A	127	60.057	31.509	58.331	1.00	28.64
ATOM	1045	CB	GLN	A	127	59.815	29.441	60.584	1.00	34.08
ATOM	1046	CG	GLN	A	127	58.761	28.522	61.214	1.00	40.26
ATOM	1047	CD	GLN	A	127	58.758	28.603	62.722	1.00	41.02
ATOM	1048	OE1	GLN	A	127	59.767	28.319	63.360	1.00	43.41
ATOM	1049	NE2	GLN	A	127	57.628	29.003	63.294	1.00	45.74
ATOM	1050	N	LYS	A	128	61.925	30.275	58.015	1.00	30.38
ATOM	1051	CA	LYS	A	128	62.733	31.371	57.449	1.00	33.35
ATOM	1052	C	LYS	A	128	63.452	30.923	56.191	1.00	26.98
ATOM	1053	O	LYS	A	128	64.059	29.872	56.175	1.00	26.69
ATOM	1054	CB	LYS	A	128	63.761	31.857	58.481	1.00	32.67
ATOM	1055	CG	LYS	A	128	63.168	32.830	59.483	1.00	40.12
ATOM	1056	CD	LYS	A	128	64.055	33.017	60.694	1.00	46.31
ATOM	1057	CE	LYS	A	128	63.381	33.939	61.717	1.00	49.48
ATOM	1058	NZ	LYS	A	128	64.329	34.401	62.776	1.00	49.69
ATOM	1059	N	GLU	A	129	63.375	31.725	55.137	1.00	26.51
ATOM	1060	CA	GLU	A	129	64.084	31.448	53.881	1.00	27.16
ATOM	1061	C	GLU	A	129	65.546	31.034	54.099	1.00	27.84
ATOM	1062	O	GLU	A	129	66.048	30.082	53.484	1.00	27.85
ATOM	1063	CB	GLU	A	129	64.028	32.696	52.973	1.00	28.24
ATOM	1064	CG	GLU	A	129	62.675	32.999	52.330	1.00	30.95
ATOM	1065	CD	GLU	A	129	61.739	33.832	53.186	1.00	29.81
ATOM	1066	OE1	GLU	A	129	61.945	33.907	54.416	1.00	31.49
ATOM	1067	OE2	GLU	A	129	60.801	34.434	52.619	1.00	28.03
ATOM	1068	N	GLU	A	130	66.228	31.733	55.010	1.00	33.63
ATOM	1069	CA	GLU	A	130	67.688	31.606	55.172	1.00	33.03
ATOM	1070	C	GLU	A	130	68.097	30.442	56.079	1.00	34.75
ATOM	1071	O	GLU	A	130	69.285	30.087	56.150	1.00	34.36
ATOM	1072	CB	GLU	A	130	68.316	32.938	55.648	1.00	33.23
ATOM	1073	CG	GLU	A	130	67.894	33.433	57.028	1.00	32.78
ATOM	1074	CD	GLU	A	130	66.624	34.256	57.027	1.00	35.80
ATOM	1075	OE1	GLU	A	130	66.364	34.966	58.027	1.00	39.02
ATOM	1076	OE2	GLU	A	130	65.857	34.187	56.045	1.00	41.84
ATOM	1077	N	LYS	A	131	67.123	29.826	56.741	1.00	36.67
ATOM	1078	CA	LYS	A	131	67.401	28.665	57.593	1.00	38.30
ATOM	1079	C	LYS	A	131	66.648	27.442	57.095	1.00	36.19
ATOM	1080	O	LYS	A	131	65.550	27.105	57.558	1.00	34.88
ATOM	1081	CB	LYS	A	131	67.103	28.975	59.062	1.00	41.34
ATOM	1082	CG	LYS	A	131	68.134	29.955	59.674	1.00	45.05
ATOM	1083	CD	LYS	A	131	68.300	29.778	61.178	1.00	48.43
ATOM	1084	CE	LYS	A	131	69.408	30.682	61.734	1.00	50.09
ATOM	1085	NZ	LYS	A	131	68.964	31.471	62.922	1.00	50.14
ATOM	1086	N	GLU	A	132	67.270	26.798	56.119	1.00	34.42
ATOM	1087	CA	GLU	A	132	66.750	25.587	55.514	1.00	35.74
ATOM	1088	C	GLU	A	132	66.892	24.395	56.466	1.00	37.34

ATOM	1089	O	GLU	A	132	67.619	24.460	57.460	1.00 33.65
ATOM	1090	CB	GLU	A	132	67.446	25.316	54.176	1.00 34.20
ATOM	1091	CG	GLU	A	132	68.853	24.745	54.267	1.00 38.61
ATOM	1092	CD	GLU	A	132	69.952	25.792	54.436	1.00 39.48
ATOM	1093	OE1	GLU	A	132	69.668	26.973	54.719	1.00 36.98
ATOM	1094	OE2	GLU	A	132	71.122	25.412	54.291	1.00 45.87
ATOM	1095	N	MET	A	133	66.190	23.312	56.138	1.00 35.30
ATOM	1096	CA	MET	A	133	66.177	22.110	56.957	1.00 34.88
ATOM	1097	C	MET	A	133	66.792	20.981	56.178	1.00 33.80
ATOM	1098	O	MET	A	133	66.522	20.830	54.989	1.00 33.74
ATOM	1099	CB	MET	A	133	64.744	21.748	57.319	1.00 33.26
ATOM	1100	CG	MET	A	133	64.176	22.544	58.438	1.00 33.35
ATOM	1101	SD	MET	A	133	62.443	22.059	58.728	1.00 34.77
ATOM	1102	CE	MET	A	133	62.621	21.053	60.084	1.00 36.12
ATOM	1103	N	ILE	A	134	67.632	20.198	56.845	1.00 35.34
ATOM	1104	CA	ILE	A	134	68.234	19.020	56.243	1.00 37.22
ATOM	1105	C	ILE	A	134	67.722	17.787	56.974	1.00 34.26
ATOM	1106	O	ILE	A	134	67.808	17.718	58.186	1.00 36.80
ATOM	1107	CB	ILE	A	134	69.779	19.065	56.348	1.00 40.26
ATOM	1108	CG1	ILE	A	134	70.341	20.444	55.945	1.00 43.15
ATOM	1109	CG2	ILE	A	134	70.397	17.908	55.544	1.00 39.51
ATOM	1110	CD1	ILE	A	134	70.767	20.560	54.500	1.00 45.41
ATOM	1111	N	PHE	A	135	67.186	16.823	56.235	1.00 33.93
ATOM	1112	CA	PHE	A	135	66.764	15.537	56.802	1.00 36.30
ATOM	1113	C	PHE	A	135	67.762	14.494	56.339	1.00 39.30
ATOM	1114	O	PHE	A	135	67.670	13.984	55.222	1.00 38.06
ATOM	1115	CB	PHE	A	135	65.329	15.193	56.372	1.00 33.62
ATOM	1116	CG	PHE	A	135	64.340	16.272	56.728	1.00 33.99
ATOM	1117	CD1	PHE	A	135	63.905	16.420	58.022	1.00 32.90
ATOM	1118	CD2	PHE	A	135	63.897	17.171	55.776	1.00 32.67
ATOM	1119	CE1	PHE	A	135	63.017	17.430	58.355	1.00 34.12
ATOM	1120	CE2	PHE	A	135	63.007	18.176	56.113	1.00 30.63
ATOM	1121	CZ	PHE	A	135	62.586	18.310	57.397	1.00 30.45
ATOM	1122	N	GLU	A	136	68.726	14.208	57.214	1.00 43.37
ATOM	1123	CA	GLU	A	136	69.899	13.395	56.877	1.00 47.63
ATOM	1124	C	GLU	A	136	69.494	11.943	56.705	1.00 44.75
ATOM	1125	O	GLU	A	136	70.035	11.249	55.851	1.00 45.05
ATOM	1126	CB	GLU	A	136	70.990	13.499	57.971	1.00 52.42
ATOM	1127	CG	GLU	A	136	71.085	14.858	58.671	1.00 58.67
ATOM	1128	CD	GLU	A	136	72.496	15.207	59.119	1.00 64.68
ATOM	1129	OE1	GLU	A	136	72.979	14.607	60.109	1.00 68.18
ATOM	1130	OE2	GLU	A	136	73.119	16.089	58.479	1.00 69.15
ATOM	1131	N	ASP	A	137	68.530	11.504	57.514	1.00 42.45
ATOM	1132	CA	ASP	A	137	68.008	10.137	57.436	1.00 42.01
ATOM	1133	C	ASP	A	137	67.372	9.759	56.080	1.00 43.10
ATOM	1134	O	ASP	A	137	67.449	8.597	55.679	1.00 46.70
ATOM	1135	CB	ASP	A	137	67.052	9.841	58.613	1.00 40.00
ATOM	1136	CG	ASP	A	137	65.732	10.645	58.559	1.00 43.12
ATOM	1137	OD1	ASP	A	137	65.703	11.803	58.068	1.00 39.61
ATOM	1138	OD2	ASP	A	137	64.662	10.187	59.017	1.00 38.14
ATOM	1139	N	THR	A	138	66.755	10.711	55.374	1.00 42.85
ATOM	1140	CA	THR	A	138	66.156	10.412	54.053	1.00 42.62
ATOM	1141	C	THR	A	138	66.784	11.165	52.892	1.00 41.22
ATOM	1142	O	THR	A	138	66.286	11.099	51.766	1.00 41.62
ATOM	1143	CB	THR	A	138	64.617	10.641	54.034	1.00 41.82
ATOM	1144	OG1	THR	A	138	64.303	11.968	54.472	1.00 37.95
ATOM	1145	CG2	THR	A	138	63.905	9.699	55.017	1.00 41.84
ATOM	1146	N	ASN	A	139	67.873	11.872	53.168	1.00 45.49

ATOM	1147	CA	ASN	A	139	68.651	12.566	52.133	1.00 47.20
ATOM	1148	C	ASN	A	139	67.884	13.663	51.411	1.00 44.12
ATOM	1149	O	ASN	A	139	67.917	13.745	50.178	1.00 41.55
ATOM	1150	CB	ASN	A	139	69.213	11.561	51.111	1.00 49.65
ATOM	1151	CG	ASN	A	139	70.600	11.952	50.608	1.00 55.72
ATOM	1152	OD1	ASN	A	139	70.827	12.077	49.394	1.00 56.14
ATOM	1153	ND2	ASN	A	139	71.539	12.141	51.542	1.00 53.88
ATOM	1154	N	LEU	A	140	67.190	14.501	52.180	1.00 40.44
ATOM	1155	CA	LEU	A	140	66.466	15.627	51.612	1.00 37.75
ATOM	1156	C	LEU	A	140	66.819	16.927	52.288	1.00 37.73
ATOM	1157	O	LEU	A	140	67.133	16.955	53.469	1.00 37.57
ATOM	1158	CB	LEU	A	140	64.964	15.408	51.703	1.00 35.68
ATOM	1159	CG	LEU	A	140	64.456	14.197	50.920	1.00 37.88
ATOM	1160	CD1	LEU	A	140	63.131	13.764	51.497	1.00 38.08
ATOM	1161	CD2	LEU	A	140	64.330	14.516	49.425	1.00 40.15
ATOM	1162	N	LYS	A	141	66.778	17.996	51.499	1.00 37.25
ATOM	1163	CA	LYS	A	141	66.857	19.355	51.980	1.00 36.58
ATOM	1164	C	LYS	A	141	65.536	20.017	51.659	1.00 33.66
ATOM	1165	O	LYS	A	141	64.922	19.709	50.645	1.00 30.42
ATOM	1166	CB	LYS	A	141	67.982	20.095	51.256	1.00 41.02
ATOM	1167	CG	LYS	A	141	68.130	21.559	51.664	1.00 45.52
ATOM	1168	CD	LYS	A	141	69.555	22.076	51.460	1.00 46.16
ATOM	1169	CE	LYS	A	141	69.785	22.629	50.076	1.00 47.51
ATOM	1170	NZ	LYS	A	141	71.203	23.109	49.957	1.00 50.68
ATOM	1171	N	LEU	A	142	65.121	20.944	52.514	1.00 30.65
ATOM	1172	CA	LEU	A	142	63.871	21.664	52.356	1.00 30.54
ATOM	1173	C	LEU	A	142	64.083	23.155	52.644	1.00 29.07
ATOM	1174	O	LEU	A	142	64.603	23.522	53.697	1.00 27.92
ATOM	1175	CB	LEU	A	142	62.844	21.095	53.342	1.00 31.26
ATOM	1176	CG	LEU	A	142	61.456	21.702	53.417	1.00 29.15
ATOM	1177	CD1	LEU	A	142	60.715	21.477	52.097	1.00 31.49
ATOM	1178	CD2	LEU	A	142	60.676	21.086	54.576	1.00 26.99
ATOM	1179	N	THR	A	143	63.599	24.003	51.742	1.00 30.42
ATOM	1180	CA	THR	A	143	63.812	25.449	51.808	1.00 26.87
ATOM	1181	C	THR	A	143	62.512	26.195	51.640	1.00 25.51
ATOM	1182	O	THR	A	143	61.757	25.946	50.709	1.00 27.09
ATOM	1183	CB	THR	A	143	64.787	25.857	50.664	1.00 29.15
ATOM	1184	OG1	THR	A	143	65.962	25.047	50.743	1.00 29.13
ATOM	1185	CG2	THR	A	143	65.295	27.292	50.837	1.00 31.43
ATOM	1186	N	LEU	A	144	62.233	27.108	52.553	1.00 24.97
ATOM	1187	CA	LEU	A	144	61.146	28.032	52.385	1.00 25.26
ATOM	1188	C	LEU	A	144	61.511	29.055	51.286	1.00 29.95
ATOM	1189	O	LEU	A	144	62.464	29.826	51.432	1.00 31.10
ATOM	1190	CB	LEU	A	144	60.885	28.736	53.705	1.00 27.54
ATOM	1191	CG	LEU	A	144	59.827	29.820	53.656	1.00 27.82
ATOM	1192	CD1	LEU	A	144	58.487	29.210	53.283	1.00 31.82
ATOM	1193	CD2	LEU	A	144	59.759	30.513	54.977	1.00 27.49
ATOM	1194	N	ILE	A	145	60.739	29.053	50.203	1.00 32.40
ATOM	1195	CA	ILE	A	145	60.906	29.972	49.068	1.00 30.54
ATOM	1196	C	ILE	A	145	60.122	31.250	49.246	1.00 30.05
ATOM	1197	O	ILE	A	145	60.586	32.331	48.913	1.00 31.49
ATOM	1198	CB	ILE	A	145	60.443	29.274	47.791	1.00 32.14
ATOM	1199	CG1	ILE	A	145	61.303	28.044	47.537	1.00 34.16
ATOM	1200	CG2	ILE	A	145	60.468	30.206	46.577	1.00 31.43
ATOM	1201	CD1	ILE	A	145	62.792	28.298	47.576	1.00 37.81
ATOM	1202	N	SER	A	146	58.916	31.123	49.756	1.00 30.51
ATOM	1203	CA	SER	A	146	58.053	32.263	49.941	1.00 31.90
ATOM	1204	C	SER	A	146	56.887	31.862	50.814	1.00 34.24

ATOM	1205	O	SER	A	146	56.577	30.676	50.963	1.00 34.61
ATOM	1206	CB	SER	A	146	57.510	32.748	48.601	1.00 34.65
ATOM	1207	OG	SER	A	146	56.477	31.885	48.152	1.00 36.04
ATOM	1208	N	GLU	A	147	56.216	32.868	51.344	1.00 34.68
ATOM	1209	CA	GLU	A	147	55.179	32.676	52.336	1.00 37.65
ATOM	1210	C	GLU	A	147	54.228	33.848	52.217	1.00 40.62
ATOM	1211	O	GLU	A	147	54.655	34.997	52.214	1.00 43.39
ATOM	1212	CB	GLU	A	147	55.808	32.617	53.732	1.00 39.51
ATOM	1213	CG	GLU	A	147	54.842	32.766	54.894	1.00 41.67
ATOM	1214	CD	GLU	A	147	55.473	32.406	56.226	1.00 42.88
ATOM	1215	OE1	GLU	A	147	55.544	31.209	56.547	1.00 46.46
ATOM	1216	OE2	GLU	A	147	55.895	33.313	56.964	1.00 44.93
ATOM	1217	N	ASP	A	148	52.936	33.556	52.150	1.00 40.95
ATOM	1218	CA	ASP	A	148	51.919	34.570	52.011	1.00 37.92
ATOM	1219	C	ASP	A	148	50.864	34.328	53.083	1.00 39.88
ATOM	1220	O	ASP	A	148	50.037	33.408	52.969	1.00 32.95
ATOM	1221	CB	ASP	A	148	51.335	34.509	50.605	1.00 43.73
ATOM	1222	CG	ASP	A	148	50.246	35.545	50.362	1.00 47.38
ATOM	1223	OD1	ASP	A	148	50.191	36.577	51.073	1.00 49.14
ATOM	1224	OD2	ASP	A	148	49.396	35.388	49.463	1.00 50.53
ATOM	1225	N	ILE	A	149	50.910	35.162	54.128	1.00 36.98
ATOM	1226	CA	ILE	A	149	50.009	35.055	55.265	1.00 37.31
ATOM	1227	C	ILE	A	149	48.723	35.843	55.006	1.00 39.45
ATOM	1228	O	ILE	A	149	48.749	37.056	54.802	1.00 41.38
ATOM	1229	CB	ILE	A	149	50.698	35.565	56.541	1.00 38.10
ATOM	1230	CG1	ILE	A	149	52.047	34.857	56.742	1.00 40.59
ATOM	1231	CG2	ILE	A	149	49.789	35.382	57.748	1.00 38.89
ATOM	1232	CD1	ILE	A	149	52.857	35.334	57.940	1.00 41.10
ATOM	1233	N	LYS	A	150	47.601	35.135	55.016	1.00 36.60
ATOM	1234	CA	LYS	A	150	46.286	35.743	54.929	1.00 36.95
ATOM	1235	C	LYS	A	150	45.510	35.490	56.214	1.00 36.61
ATOM	1236	O	LYS	A	150	45.993	34.827	57.139	1.00 36.14
ATOM	1237	CB	LYS	A	150	45.531	35.231	53.692	1.00 38.49
ATOM	1238	CG	LYS	A	150	46.350	35.379	52.394	1.00 43.90
ATOM	1239	CD	LYS	A	150	45.515	35.799	51.170	1.00 51.08
ATOM	1240	CE	LYS	A	150	45.565	37.321	50.910	1.00 55.46
ATOM	1241	NZ	LYS	A	150	45.129	37.689	49.512	1.00 57.60
ATOM	1242	N	SER	A	151	44.300	36.028	56.272	1.00 37.57
ATOM	1243	CA	SER	A	151	43.549	36.067	57.519	1.00 39.40
ATOM	1244	C	SER	A	151	43.190	34.674	58.020	1.00 39.24
ATOM	1245	O	SER	A	151	43.321	34.401	59.211	1.00 36.49
ATOM	1246	CB	SER	A	151	42.283	36.926	57.368	1.00 41.83
ATOM	1247	OG	SER	A	151	42.038	37.267	56.013	1.00 50.33
ATOM	1248	N	TYR	A	152	42.767	33.788	57.114	1.00 38.17
ATOM	1249	CA	TYR	A	152	42.261	32.478	57.513	1.00 41.75
ATOM	1250	C	TYR	A	152	43.190	31.317	57.146	1.00 39.57
ATOM	1251	O	TYR	A	152	42.959	30.185	57.564	1.00 36.58
ATOM	1252	CB	TYR	A	152	40.848	32.251	56.945	1.00 46.83
ATOM	1253	CG	TYR	A	152	39.816	33.184	57.546	1.00 56.16
ATOM	1254	CD1	TYR	A	152	39.525	34.415	56.944	1.00 61.10
ATOM	1255	CD2	TYR	A	152	39.146	32.856	58.732	1.00 60.48
ATOM	1256	CE1	TYR	A	152	38.588	35.291	57.497	1.00 64.02
ATOM	1257	CE2	TYR	A	152	38.208	33.729	59.296	1.00 65.39
ATOM	1258	CZ	TYR	A	152	37.933	34.943	58.669	1.00 66.00
ATOM	1259	OH	TYR	A	152	37.007	35.811	59.206	1.00 71.91
ATOM	1260	N	TYR	A	153	44.230	31.592	56.369	1.00 37.51
ATOM	1261	CA	TYR	A	153	45.165	30.559	55.973	1.00 35.07
ATOM	1262	C	TYR	A	153	46.472	31.154	55.481	1.00 31.45

ATOM	1263	O	TYR	A	153	46.514	32.318	55.122	1.00 29.67
ATOM	1264	CB	TYR	A	153	44.538	29.674	54.880	1.00 36.12
ATOM	1265	CG	TYR	A	153	44.435	30.333	53.529	1.00 38.08
ATOM	1266	CD1	TYR	A	153	43.311	31.085	53.180	1.00 44.22
ATOM	1267	CD2	TYR	A	153	45.449	30.194	52.591	1.00 41.96
ATOM	1268	CE1	TYR	A	153	43.213	31.695	51.933	1.00 46.04
ATOM	1269	CE2	TYR	A	153	45.362	30.801	51.346	1.00 46.25
ATOM	1270	CZ	TYR	A	153	44.252	31.556	51.027	1.00 48.63
ATOM	1271	OH	TYR	A	153	44.196	32.146	49.781	1.00 55.82
ATOM	1272	N	THR	A	154	47.523	30.336	55.443	1.00 24.30
ATOM	1273	CA	THR	A	154	48.794	30.726	54.845	1.00 27.50
ATOM	1274	C	THR	A	154	49.209	29.758	53.718	1.00 26.17
ATOM	1275	O	THR	A	154	48.947	28.566	53.796	1.00 28.65
ATOM	1276	CB	THR	A	154	49.857	30.786	55.956	1.00 26.73
ATOM	1277	OG1	THR	A	154	49.487	31.798	56.899	1.00 27.84
ATOM	1278	CG2	THR	A	154	51.191	31.230	55.441	1.00 27.67
ATOM	1279	N	VAL	A	155	49.816	30.286	52.658	1.00 26.64
ATOM	1280	CA	VAL	A	155	50.359	29.475	51.569	1.00 25.67
ATOM	1281	C	VAL	A	155	51.839	29.717	51.506	1.00 27.10
ATOM	1282	O	VAL	A	155	52.289	30.875	51.433	1.00 30.22
ATOM	1283	CB	VAL	A	155	49.787	29.857	50.174	1.00 27.77
ATOM	1284	CG1	VAL	A	155	50.170	28.802	49.128	1.00 32.39
ATOM	1285	CG2	VAL	A	155	48.332	30.020	50.238	1.00 35.84
ATOM	1286	N	ARG	A	156	52.597	28.633	51.494	1.00 25.08
ATOM	1287	CA	ARG	A	156	54.028	28.689	51.385	1.00 26.10
ATOM	1288	C	ARG	A	156	54.488	27.919	50.151	1.00 29.29
ATOM	1289	O	ARG	A	156	53.908	26.917	49.778	1.00 28.61
ATOM	1290	CB	ARG	A	156	54.675	28.110	52.642	1.00 27.56
ATOM	1291	CG	ARG	A	156	54.185	28.760	53.943	1.00 30.11
ATOM	1292	CD	ARG	A	156	54.898	28.293	55.213	1.00 31.28
ATOM	1293	NE	ARG	A	156	54.310	28.872	56.431	1.00 32.23
ATOM	1294	CZ	ARG	A	156	53.240	28.402	57.079	1.00 30.33
ATOM	1295	NH1	ARG	A	156	52.609	27.313	56.676	1.00 33.27
ATOM	1296	NH2	ARG	A	156	52.799	29.024	58.165	1.00 32.37
ATOM	1297	N	GLN	A	157	55.526	28.415	49.500	1.00 27.76
ATOM	1298	CA	GLN	A	157	56.202	27.651	48.491	1.00 26.23
ATOM	1299	C	GLN	A	157	57.474	27.135	49.121	1.00 25.68
ATOM	1300	O	GLN	A	157	58.165	27.842	49.831	1.00 27.03
ATOM	1301	CB	GLN	A	157	56.438	28.528	47.266	1.00 28.63
ATOM	1302	CG	GLN	A	157	57.220	27.861	46.190	1.00 35.97
ATOM	1303	CD	GLN	A	157	57.376	28.715	44.949	1.00 38.81
ATOM	1304	OE1	GLN	A	157	56.665	29.716	44.776	1.00 39.09
ATOM	1305	NE2	GLN	A	157	58.311	28.322	44.080	1.00 37.90
ATOM	1306	N	LEU	A	158	57.761	25.867	48.892	1.00 26.47
ATOM	1307	CA	LEU	A	158	58.905	25.202	49.481	1.00 26.97
ATOM	1308	C	LEU	A	158	59.626	24.509	48.366	1.00 26.82
ATOM	1309	O	LEU	A	158	59.021	24.177	47.349	1.00 30.23
ATOM	1310	CB	LEU	A	158	58.474	24.169	50.528	1.00 25.90
ATOM	1311	CG	LEU	A	158	57.530	24.616	51.648	1.00 28.92
ATOM	1312	CD1	LEU	A	158	56.875	23.410	52.328	1.00 31.53
ATOM	1313	CD2	LEU	A	158	58.277	25.462	52.668	1.00 32.05
ATOM	1314	N	GLU	A	159	60.923	24.310	48.534	1.00 28.10
ATOM	1315	CA	GLU	A	159	61.701	23.530	47.585	1.00 30.18
ATOM	1316	C	GLU	A	159	62.301	22.366	48.320	1.00 30.18
ATOM	1317	O	GLU	A	159	62.841	22.529	49.400	1.00 30.29
ATOM	1318	CB	GLU	A	159	62.803	24.358	46.938	1.00 31.30
ATOM	1319	CG	GLU	A	159	63.487	23.633	45.789	1.00 40.31
ATOM	1320	CD	GLU	A	159	64.505	24.503	45.054	1.00 44.60

ATOM	1321	OE1	GLU	A	159	65.664	24.081	44.931	1.00 48.32
ATOM	1322	OE2	GLU	A	159	64.144	25.601	44.603	1.00 49.88
ATOM	1323	N	LEU	A	160	62.195	21.197	47.710	1.00 31.42
ATOM	1324	CA	LEU	A	160	62.685	19.953	48.249	1.00 35.20
ATOM	1325	C	LEU	A	160	63.812	19.485	47.335	1.00 39.41
ATOM	1326	O	LEU	A	160	63.610	19.381	46.134	1.00 39.24
ATOM	1327	CB	LEU	A	160	61.511	18.967	48.221	1.00 38.43
ATOM	1328	CG	LEU	A	160	61.364	17.751	49.128	1.00 38.81
ATOM	1329	CD1	LEU	A	160	59.970	17.156	48.856	1.00 34.93
ATOM	1330	CD2	LEU	A	160	61.552	18.064	50.614	1.00 34.53
ATOM	1331	N	GLU	A	161	64.997	19.221	47.886	1.00 44.11
ATOM	1332	CA	GLU	A	161	66.130	18.742	47.097	1.00 48.70
ATOM	1333	C	GLU	A	161	66.536	17.335	47.516	1.00 49.27
ATOM	1334	O	GLU	A	161	66.820	17.090	48.683	1.00 47.95
ATOM	1335	CB	GLU	A	161	67.339	19.683	47.242	1.00 51.56
ATOM	1336	CG	GLU	A	161	68.406	19.487	46.163	1.00 54.78
ATOM	1337	CD	GLU	A	161	69.724	20.166	46.481	1.00 56.70
ATOM	1338	OE1	GLU	A	161	69.708	21.310	46.956	1.00 57.99
ATOM	1339	OE2	GLU	A	161	70.785	19.552	46.244	1.00 64.66
ATOM	1340	N	ASN	A	162	66.548	16.405	46.568	1.00 54.08
ATOM	1341	CA	ASN	A	162	67.179	15.107	46.789	1.00 56.50
ATOM	1342	C	ASN	A	162	68.695	15.304	46.821	1.00 58.99
ATOM	1343	O	ASN	A	162	69.323	15.397	45.779	1.00 61.68
ATOM	1344	CB	ASN	A	162	66.775	14.119	45.693	1.00 57.69
ATOM	1345	CG	ASN	A	162	67.313	12.711	45.939	1.00 59.88
ATOM	1346	OD1	ASN	A	162	68.520	12.511	46.145	1.00 58.62
ATOM	1347	ND2	ASN	A	162	66.413	11.728	45.918	1.00 56.89
ATOM	1348	N	LEU	A	163	69.267	15.380	48.020	1.00 59.13
ATOM	1349	CA	LEU	A	163	70.678	15.724	48.202	1.00 63.54
ATOM	1350	C	LEU	A	163	71.705	14.880	47.410	1.00 67.69
ATOM	1351	O	LEU	A	163	72.784	15.382	47.075	1.00 66.84
ATOM	1352	CB	LEU	A	163	71.040	15.688	49.696	1.00 62.10
ATOM	1353	CG	LEU	A	163	70.544	16.860	50.554	1.00 62.17
ATOM	1354	CD1	LEU	A	163	71.139	16.782	51.945	1.00 60.89
ATOM	1355	CD2	LEU	A	163	70.853	18.219	49.914	1.00 63.68
ATOM	1356	N	THR	A	164	71.381	13.619	47.125	1.00 71.50
ATOM	1357	CA	THR	A	164	72.294	12.743	46.388	1.00 75.23
ATOM	1358	C	THR	A	164	72.340	13.146	44.912	1.00 76.98
ATOM	1359	O	THR	A	164	73.420	13.347	44.353	1.00 78.26
ATOM	1360	CB	THR	A	164	71.869	11.255	46.529	1.00 76.31
ATOM	1361	OG1	THR	A	164	72.214	10.768	47.831	1.00 77.12
ATOM	1362	CG2	THR	A	164	72.671	10.347	45.589	1.00 77.98
ATOM	1363	N	THR	A	165	71.155	13.280	44.309	1.00 77.26
ATOM	1364	CA	THR	A	165	71.001	13.529	42.871	1.00 75.84
ATOM	1365	C	THR	A	165	70.880	15.016	42.483	1.00 73.80
ATOM	1366	O	THR	A	165	70.856	15.342	41.299	1.00 75.32
ATOM	1367	CB	THR	A	165	69.759	12.769	42.347	1.00 76.34
ATOM	1368	OG1	THR	A	165	68.565	13.344	42.894	1.00 78.11
ATOM	1369	CG2	THR	A	165	69.733	11.322	42.853	1.00 76.64
ATOM	1370	N	GLN	A	166	70.801	15.900	43.476	1.00 69.63
ATOM	1371	CA	GLN	A	166	70.591	17.348	43.288	1.00 66.56
ATOM	1372	C	GLN	A	166	69.306	17.803	42.546	1.00 61.69
ATOM	1373	O	GLN	A	166	69.146	19.003	42.296	1.00 58.47
ATOM	1374	CB	GLN	A	166	71.836	18.000	42.656	1.00 69.16
ATOM	1375	CG	GLN	A	166	73.145	17.762	43.440	1.00 71.16
ATOM	1376	CD	GLN	A	166	74.080	18.970	43.451	1.00 72.58
ATOM	1377	OE1	GLN	A	166	74.818	19.185	44.415	1.00 74.04
ATOM	1378	NE2	GLN	A	166	74.052	19.751	42.386	1.00 74.28

ATOM	1379	N	GLU	A	167	68.390	16.881	42.226	1.00 57.39
ATOM	1380	CA	GLU	A	167	67.062	17.257	41.692	1.00 57.78
ATOM	1381	C	GLU	A	167	66.280	18.111	42.705	1.00 53.55
ATOM	1382	O	GLU	A	167	66.476	17.992	43.914	1.00 51.23
ATOM	1383	CB	GLU	A	167	66.178	16.035	41.387	1.00 59.44
ATOM	1384	CG	GLU	A	167	66.720	14.998	40.420	1.00 64.57
ATOM	1385	CD	GLU	A	167	66.137	13.621	40.700	1.00 68.48
ATOM	1386	OE1	GLU	A	167	64.902	13.441	40.554	1.00 71.00
ATOM	1387	OE2	GLU	A	167	66.909	12.723	41.093	1.00 70.28
ATOM	1388	N	THR	A	168	65.383	18.948	42.200	1.00 50.37
ATOM	1389	CA	THR	A	168	64.550	19.809	43.034	1.00 47.15
ATOM	1390	C	THR	A	168	63.097	19.658	42.641	1.00 45.69
ATOM	1391	O	THR	A	168	62.799	19.382	41.487	1.00 46.95
ATOM	1392	CB	THR	A	168	64.922	21.271	42.843	1.00 46.52
ATOM	1393	OG1	THR	A	168	64.870	21.595	41.446	1.00 45.51
ATOM	1394	CG2	THR	A	168	66.361	21.534	43.269	1.00 46.99
ATOM	1395	N	ARG	A	169	62.199	19.873	43.594	1.00 41.85
ATOM	1396	CA	ARG	A	169	60.769	19.945	43.309	1.00 39.92
ATOM	1397	C	ARG	A	169	60.167	21.092	44.097	1.00 36.00
ATOM	1398	O	ARG	A	169	60.542	21.301	45.234	1.00 36.05
ATOM	1399	CB	ARG	A	169	60.091	18.631	43.678	1.00 41.63
ATOM	1400	CG	ARG	A	169	60.529	17.453	42.803	1.00 47.97
ATOM	1401	CD	ARG	A	169	60.037	16.084	43.258	1.00 53.84
ATOM	1402	NE	ARG	A	169	59.410	15.355	42.159	1.00 61.38
ATOM	1403	CZ	ARG	A	169	58.147	15.510	41.770	1.00 65.71
ATOM	1404	NH1	ARG	A	169	57.685	14.806	40.743	1.00 69.78
ATOM	1405	NH2	ARG	A	169	57.334	16.350	42.402	1.00 66.33
ATOM	1406	N	GLU	A	170	59.266	21.842	43.473	1.00 31.05
ATOM	1407	CA	GLU	A	170	58.476	22.866	44.130	1.00 34.08
ATOM	1408	C	GLU	A	170	57.255	22.215	44.822	1.00 32.33
ATOM	1409	O	GLU	A	170	56.479	21.527	44.184	1.00 31.31
ATOM	1410	CB	GLU	A	170	58.004	23.911	43.091	1.00 38.29
ATOM	1411	CG	GLU	A	170	57.032	24.969	43.634	1.00 47.97
ATOM	1412	CD	GLU	A	170	56.421	25.896	42.573	1.00 52.73
ATOM	1413	OE1	GLU	A	170	56.787	25.827	41.372	1.00 60.61
ATOM	1414	OE2	GLU	A	170	55.562	26.720	42.954	1.00 55.45
ATOM	1415	N	ILE	A	171	57.093	22.444	46.122	1.00 31.01
ATOM	1416	CA	ILE	A	171	55.911	22.019	46.866	1.00 25.68
ATOM	1417	C	ILE	A	171	55.143	23.212	47.391	1.00 24.75
ATOM	1418	O	ILE	A	171	55.738	24.165	47.917	1.00 27.08
ATOM	1419	CB	ILE	A	171	56.324	21.139	48.055	1.00 27.41
ATOM	1420	CG1	ILE	A	171	57.228	19.983	47.605	1.00 28.28
ATOM	1421	CG2	ILE	A	171	55.093	20.620	48.752	1.00 31.23
ATOM	1422	CD1	ILE	A	171	56.592	19.051	46.602	1.00 30.57
ATOM	1423	N	LEU	A	172	53.821	23.172	47.286	1.00 22.95
ATOM	1424	CA	LEU	A	172	52.987	24.192	47.915	1.00 24.79
ATOM	1425	C	LEU	A	172	52.448	23.652	49.233	1.00 27.69
ATOM	1426	O	LEU	A	172	51.962	22.526	49.287	1.00 27.52
ATOM	1427	CB	LEU	A	172	51.840	24.622	46.980	1.00 25.78
ATOM	1428	CG	LEU	A	172	52.298	25.213	45.637	1.00 28.93
ATOM	1429	CD1	LEU	A	172	51.119	25.492	44.738	1.00 33.95
ATOM	1430	CD2	LEU	A	172	53.075	26.505	45.846	1.00 33.75
ATOM	1431	N	HIS	A	173	52.550	24.467	50.279	1.00 25.46
ATOM	1432	CA	HIS	A	173	52.099	24.163	51.619	1.00 25.40
ATOM	1433	C	HIS	A	173	50.884	25.038	51.895	1.00 27.85
ATOM	1434	O	HIS	A	173	50.992	26.255	51.960	1.00 25.57
ATOM	1435	CB	HIS	A	173	53.219	24.451	52.635	1.00 27.52
ATOM	1436	CG	HIS	A	173	52.962	23.882	54.003	1.00 28.74

ATOM	1437	ND1	HIS	A	173	52.361	24.604	55.009	1.00 32.01
ATOM	1438	CD2	HIS	A	173	53.234	22.666	54.531	1.00 28.14
ATOM	1439	CE1	HIS	A	173	52.263	23.856	56.094	1.00 31.02
ATOM	1440	NE2	HIS	A	173	52.776	22.670	55.828	1.00 25.05
ATOM	1441	N	PHE	A	174	49.722	24.416	52.052	1.00 23.77
ATOM	1442	CA	PHE	A	174	48.488	25.129	52.292	1.00 23.14
ATOM	1443	C	PHE	A	174	48.088	24.933	53.718	1.00 25.18
ATOM	1444	O	PHE	A	174	47.684	23.847	54.099	1.00 25.93
ATOM	1445	CB	PHE	A	174	47.398	24.634	51.357	1.00 23.57
ATOM	1446	CG	PHE	A	174	47.553	25.144	49.978	1.00 26.89
ATOM	1447	CD1	PHE	A	174	47.054	26.388	49.633	1.00 31.06
ATOM	1448	CD2	PHE	A	174	48.221	24.407	49.030	1.00 29.99
ATOM	1449	CE1	PHE	A	174	47.233	26.882	48.353	1.00 33.42
ATOM	1450	CE2	PHE	A	174	48.396	24.907	47.767	1.00 30.05
ATOM	1451	CZ	PHE	A	174	47.916	26.138	47.438	1.00 28.42
ATOM	1452	N	HIS	A	175	48.179	25.998	54.509	1.00 26.31
ATOM	1453	CA	HIS	A	175	48.073	25.891	55.949	1.00 26.03
ATOM	1454	C	HIS	A	175	46.837	26.628	56.434	1.00 26.92
ATOM	1455	O	HIS	A	175	46.803	27.846	56.488	1.00 30.80
ATOM	1456	CB	HIS	A	175	49.373	26.377	56.597	1.00 26.25
ATOM	1457	CG	HIS	A	175	49.434	26.186	58.079	1.00 23.87
ATOM	1458	ND1	HIS	A	175	50.325	26.874	58.877	1.00 21.48
ATOM	1459	CD2	HIS	A	175	48.735	25.374	58.910	1.00 26.98
ATOM	1460	CE1	HIS	A	175	50.164	26.503	60.135	1.00 25.22
ATOM	1461	NE2	HIS	A	175	49.203	25.596	60.186	1.00 24.19
ATOM	1462	N	TYR	A	176	45.787	25.869	56.738	1.00 27.05
ATOM	1463	CA	TYR	A	176	44.594	26.441	57.306	1.00 28.27
ATOM	1464	C	TYR	A	176	44.851	26.679	58.777	1.00 29.68
ATOM	1465	O	TYR	A	176	45.037	25.740	59.532	1.00 28.65
ATOM	1466	CB	TYR	A	176	43.400	25.532	57.116	1.00 29.77
ATOM	1467	CG	TYR	A	176	42.088	26.207	57.393	1.00 28.59
ATOM	1468	CD1	TYR	A	176	41.374	25.942	58.551	1.00 32.85
ATOM	1469	CD2	TYR	A	176	41.552	27.096	56.484	1.00 28.77
ATOM	1470	CE1	TYR	A	176	40.143	26.570	58.799	1.00 35.34
ATOM	1471	CE2	TYR	A	176	40.334	27.717	56.714	1.00 33.98
ATOM	1472	CZ	TYR	A	176	39.634	27.454	57.869	1.00 32.54
ATOM	1473	OH	TYR	A	176	38.437	28.080	58.072	1.00 34.52
ATOM	1474	N	THR	A	177	44.841	27.949	59.173	1.00 32.09
ATOM	1475	CA	THR	A	177	45.247	28.369	60.514	1.00 33.80
ATOM	1476	C	THR	A	177	44.111	28.787	61.469	1.00 34.23
ATOM	1477	O	THR	A	177	44.388	29.192	62.602	1.00 39.48
ATOM	1478	CB	THR	A	177	46.229	29.542	60.376	1.00 33.44
ATOM	1479	OG1	THR	A	177	45.597	30.629	59.676	1.00 29.45
ATOM	1480	CG2	THR	A	177	47.426	29.157	59.495	1.00 28.83
ATOM	1481	N	THR	A	178	42.853	28.682	61.055	1.00 35.48
ATOM	1482	CA	THR	A	178	41.752	29.239	61.860	1.00 36.85
ATOM	1483	C	THR	A	178	40.661	28.270	62.290	1.00 36.36
ATOM	1484	O	THR	A	178	39.655	28.701	62.837	1.00 41.00
ATOM	1485	CB	THR	A	178	41.113	30.430	61.130	1.00 38.52
ATOM	1486	OG1	THR	A	178	40.857	30.078	59.768	1.00 39.50
ATOM	1487	CG2	THR	A	178	42.102	31.614	61.060	1.00 39.30
ATOM	1488	N	TRP	A	179	40.849	26.974	62.074	1.00 36.04
ATOM	1489	CA	TRP	A	179	39.917	25.989	62.619	1.00 36.03
ATOM	1490	C	TRP	A	179	39.908	26.136	64.143	1.00 35.88
ATOM	1491	O	TRP	A	179	40.960	26.030	64.783	1.00 38.24
ATOM	1492	CB	TRP	A	179	40.320	24.552	62.238	1.00 32.03
ATOM	1493	CG	TRP	A	179	39.235	23.560	62.491	1.00 32.00
ATOM	1494	CD1	TRP	A	179	38.794	23.135	63.697	1.00 33.75

ATOM	1495	CD2	TRP	A	179	38.443	22.866	61.509	1.00 29.81
ATOM	1496	NE1	TRP	A	179	37.775	22.227	63.545	1.00 36.67
ATOM	1497	CE2	TRP	A	179	37.539	22.039	62.210	1.00 34.91
ATOM	1498	CE3	TRP	A	179	38.413	22.853	60.111	1.00 32.08
ATOM	1499	CZ2	TRP	A	179	36.614	21.212	61.566	1.00 35.91
ATOM	1500	CZ3	TRP	A	179	37.493	22.023	59.460	1.00 30.25
ATOM	1501	CH2	TRP	A	179	36.603	21.222	60.190	1.00 36.85
ATOM	1502	N	PRO	A	180	38.740	26.345	64.738	1.00 37.20
ATOM	1503	CA	PRO	A	180	38.683	26.624	66.185	1.00 38.24
ATOM	1504	C	PRO	A	180	39.171	25.439	67.020	1.00 36.65
ATOM	1505	O	PRO	A	180	39.023	24.290	66.613	1.00 36.67
ATOM	1506	CB	PRO	A	180	37.194	26.907	66.441	1.00 37.11
ATOM	1507	CG	PRO	A	180	36.475	26.197	65.334	1.00 38.41
ATOM	1508	CD	PRO	A	180	37.398	26.288	64.129	1.00 37.33
ATOM	1509	N	ASP	A	181	39.749	25.730	68.178	1.00 39.69
ATOM	1510	CA	ASP	A	181	40.157	24.698	69.123	1.00 42.88
ATOM	1511	C	ASP	A	181	39.020	23.744	69.460	1.00 41.80
ATOM	1512	O	ASP	A	181	39.243	22.543	69.561	1.00 45.13
ATOM	1513	CB	ASP	A	181	40.700	25.326	70.414	1.00 46.18
ATOM	1514	CG	ASP	A	181	42.201	25.576	70.368	1.00 49.21
ATOM	1515	OD1	ASP	A	181	42.857	25.191	69.371	1.00 51.80
ATOM	1516	OD2	ASP	A	181	42.814	26.151	71.296	1.00 52.55
ATOM	1517	N	PHE	A	182	37.810	24.273	69.629	1.00 42.38
ATOM	1518	CA	PHE	A	182	36.635	23.454	69.943	1.00 44.84
ATOM	1519	C	PHE	A	182	35.550	23.631	68.881	1.00 45.23
ATOM	1520	O	PHE	A	182	35.287	24.733	68.415	1.00 45.26
ATOM	1521	CB	PHE	A	182	36.082	23.791	71.341	1.00 45.04
ATOM	1522	CG	PHE	A	182	36.969	23.323	72.471	1.00 49.01
ATOM	1523	CD1	PHE	A	182	36.824	22.046	73.005	1.00 49.36
ATOM	1524	CD2	PHE	A	182	37.959	24.152	72.989	1.00 50.26
ATOM	1525	CE1	PHE	A	182	37.648	21.607	74.040	1.00 50.70
ATOM	1526	CE2	PHE	A	182	38.789	23.712	74.023	1.00 51.25
ATOM	1527	CZ	PHE	A	182	38.632	22.441	74.545	1.00 49.16
ATOM	1528	N	GLY	A	183	34.926	22.527	68.500	1.00 45.75
ATOM	1529	CA	GLY	A	183	33.852	22.562	67.533	1.00 47.78
ATOM	1530	C	GLY	A	183	34.334	22.753	66.110	1.00 47.38
ATOM	1531	O	GLY	A	183	35.456	22.381	65.752	1.00 45.73
ATOM	1532	N	VAL	A	184	33.464	23.345	65.301	1.00 45.77
ATOM	1533	CA	VAL	A	184	33.718	23.551	63.887	1.00 44.43
ATOM	1534	C	VAL	A	184	33.565	25.035	63.616	1.00 45.59
ATOM	1535	O	VAL	A	184	33.027	25.751	64.461	1.00 44.78
ATOM	1536	CB	VAL	A	184	32.735	22.704	63.045	1.00 44.45
ATOM	1537	CG1	VAL	A	184	32.956	21.226	63.322	1.00 40.88
ATOM	1538	CG2	VAL	A	184	31.269	23.055	63.346	1.00 45.29
ATOM	1539	N	PRO	A	185	34.042	25.523	62.471	1.00 44.94
ATOM	1540	CA	PRO	A	185	33.797	26.928	62.106	1.00 44.70
ATOM	1541	C	PRO	A	185	32.292	27.188	62.004	1.00 46.19
ATOM	1542	O	PRO	A	185	31.550	26.280	61.623	1.00 42.32
ATOM	1543	CB	PRO	A	185	34.484	27.069	60.749	1.00 45.46
ATOM	1544	CG	PRO	A	185	35.485	25.917	60.694	1.00 44.08
ATOM	1545	CD	PRO	A	185	34.820	24.806	61.445	1.00 43.98
ATOM	1546	N	GLU	A	186	31.836	28.379	62.378	1.00 50.16
ATOM	1547	CA	GLU	A	186	30.396	28.656	62.360	1.00 54.17
ATOM	1548	C	GLU	A	186	29.870	28.699	60.925	1.00 50.98
ATOM	1549	O	GLU	A	186	28.792	28.171	60.632	1.00 49.93
ATOM	1550	CB	GLU	A	186	30.077	29.966	63.074	1.00 59.44
ATOM	1551	CG	GLU	A	186	28.600	30.124	63.403	1.00 65.31
ATOM	1552	CD	GLU	A	186	28.330	31.335	64.283	1.00 70.87

ATOM	1553	OE1	GLU	A	186	28.812	31.351	65.441	1.00 75.04
ATOM	1554	OE2	GLU	A	186	27.641	32.271	63.817	1.00 72.57
ATOM	1555	N	SER	A	187	30.655	29.325	60.048	1.00 47.88
ATOM	1556	CA	SER	A	187	30.385	29.367	58.613	1.00 45.71
ATOM	1557	C	SER	A	187	31.494	28.638	57.814	1.00 45.42
ATOM	1558	O	SER	A	187	32.686	28.883	58.043	1.00 40.50
ATOM	1559	CB	SER	A	187	30.329	30.821	58.163	1.00 44.41
ATOM	1560	OG	SER	A	187	30.507	30.944	56.768	1.00 45.78
ATOM	1561	N	PRO	A	188	31.103	27.796	56.848	1.00 43.60
ATOM	1562	CA	PRO	A	188	32.063	27.084	55.997	1.00 43.07
ATOM	1563	C	PRO	A	188	32.758	27.951	54.960	1.00 41.00
ATOM	1564	O	PRO	A	188	33.626	27.446	54.244	1.00 38.20
ATOM	1565	CB	PRO	A	188	31.183	26.057	55.287	1.00 43.32
ATOM	1566	CG	PRO	A	188	29.891	26.726	55.172	1.00 44.98
ATOM	1567	CD	PRO	A	188	29.719	27.445	56.475	1.00 44.84
ATOM	1568	N	ALA	A	189	32.394	29.227	54.883	1.00 39.03
ATOM	1569	CA	ALA	A	189	32.904	30.115	53.848	1.00 37.90
ATOM	1570	C	ALA	A	189	34.442	30.141	53.726	1.00 35.97
ATOM	1571	O	ALA	A	189	34.974	30.046	52.620	1.00 34.80
ATOM	1572	CB	ALA	A	189	32.349	31.531	54.055	1.00 38.82
ATOM	1573	N	SER	A	190	35.168	30.284	54.830	1.00 34.20
ATOM	1574	CA	SER	A	190	36.636	30.415	54.738	1.00 31.49
ATOM	1575	C	SER	A	190	37.293	29.079	54.379	1.00 27.72
ATOM	1576	O	SER	A	190	38.306	29.027	53.688	1.00 30.72
ATOM	1577	CB	SER	A	190	37.233	30.936	56.050	1.00 32.25
ATOM	1578	OG	SER	A	190	37.062	29.998	57.103	1.00 33.72
ATOM	1579	N	PHE	A	191	36.712	28.005	54.881	1.00 28.68
ATOM	1580	CA	PHE	A	191	37.176	26.665	54.599	1.00 29.10
ATOM	1581	C	PHE	A	191	36.991	26.346	53.121	1.00 28.15
ATOM	1582	O	PHE	A	191	37.870	25.771	52.494	1.00 26.66
ATOM	1583	CB	PHE	A	191	36.388	25.668	55.447	1.00 31.55
ATOM	1584	CG	PHE	A	191	36.931	24.272	55.395	1.00 34.47
ATOM	1585	CD1	PHE	A	191	38.130	23.966	56.004	1.00 37.54
ATOM	1586	CD2	PHE	A	191	36.245	23.270	54.729	1.00 35.95
ATOM	1587	CE1	PHE	A	191	38.628	22.668	55.965	1.00 40.99
ATOM	1588	CE2	PHE	A	191	36.742	21.990	54.684	1.00 34.54
ATOM	1589	CZ	PHE	A	191	37.927	21.692	55.303	1.00 34.82
ATOM	1590	N	LEU	A	192	35.841	26.721	52.565	1.00 31.93
ATOM	1591	CA	LEU	A	192	35.586	26.533	51.132	1.00 31.68
ATOM	1592	C	LEU	A	192	36.542	27.355	50.297	1.00 31.83
ATOM	1593	O	LEU	A	192	37.108	26.873	49.311	1.00 27.47
ATOM	1594	CB	LEU	A	192	34.163	26.916	50.780	1.00 31.47
ATOM	1595	CG	LEU	A	192	33.109	25.921	51.215	1.00 34.18
ATOM	1596	CD1	LEU	A	192	31.755	26.613	51.110	1.00 35.84
ATOM	1597	CD2	LEU	A	192	33.155	24.638	50.370	1.00 32.29
ATOM	1598	N	ASN	A	193	36.731	28.603	50.702	1.00 33.12
ATOM	1599	CA	ASN	A	193	37.713	29.459	50.062	1.00 35.21
ATOM	1600	C	ASN	A	193	39.100	28.850	50.050	1.00 33.12
ATOM	1601	O	ASN	A	193	39.830	28.976	49.074	1.00 30.96
ATOM	1602	CB	ASN	A	193	37.775	30.824	50.749	1.00 40.63
ATOM	1603	CG	ASN	A	193	37.632	31.935	49.777	1.00 50.07
ATOM	1604	OD1	ASN	A	193	38.629	32.546	49.377	1.00 60.40
ATOM	1605	ND2	ASN	A	193	36.396	32.179	49.329	1.00 49.93
ATOM	1606	N	PHE	A	194	39.469	28.220	51.162	1.00 30.27
ATOM	1607	CA	PHE	A	194	40.768	27.578	51.291	1.00 28.81
ATOM	1608	C	PHE	A	194	40.816	26.381	50.331	1.00 24.31
ATOM	1609	O	PHE	A	194	41.797	26.195	49.636	1.00 24.03
ATOM	1610	CB	PHE	A	194	41.005	27.182	52.766	1.00 29.31

ATOM	1611	CG	PHE	A	194	42.205	26.305	53.001	1.00	26.73
ATOM	1612	CD1	PHE	A	194	43.466	26.852	53.082	1.00	25.58
ATOM	1613	CD2	PHE	A	194	42.051	24.930	53.201	1.00	25.09
ATOM	1614	CE1	PHE	A	194	44.566	26.057	53.320	1.00	24.03
ATOM	1615	CE2	PHE	A	194	43.137	24.126	53.436	1.00	25.00
ATOM	1616	CZ	PHE	A	194	44.401	24.680	53.515	1.00	24.82
ATOM	1617	N	LEU	A	195	39.755	25.588	50.285	1.00	26.00
ATOM	1618	CA	LEU	A	195	39.680	24.467	49.344	1.00	26.38
ATOM	1619	C	LEU	A	195	39.827	24.956	47.902	1.00	25.60
ATOM	1620	O	LEU	A	195	40.530	24.350	47.113	1.00	26.37
ATOM	1621	CB	LEU	A	195	38.375	23.694	49.513	1.00	27.12
ATOM	1622	CG	LEU	A	195	38.052	22.667	48.408	1.00	28.68
ATOM	1623	CD1	LEU	A	195	39.144	21.589	48.319	1.00	24.87
ATOM	1624	CD2	LEU	A	195	36.690	22.068	48.674	1.00	29.35
ATOM	1625	N	PHE	A	196	39.204	26.077	47.570	1.00	28.88
ATOM	1626	CA	PHE	A	196	39.290	26.609	46.209	1.00	28.69
ATOM	1627	C	PHE	A	196	40.691	27.057	45.894	1.00	26.91
ATOM	1628	O	PHE	A	196	41.165	26.825	44.786	1.00	26.27
ATOM	1629	CB	PHE	A	196	38.280	27.732	45.944	1.00	27.89
ATOM	1630	CG	PHE	A	196	36.848	27.333	46.152	1.00	33.40
ATOM	1631	CD1	PHE	A	196	36.413	26.023	45.947	1.00	37.87
ATOM	1632	CD2	PHE	A	196	35.923	28.273	46.566	1.00	37.20
ATOM	1633	CE1	PHE	A	196	35.089	25.675	46.158	1.00	35.01
ATOM	1634	CE2	PHE	A	196	34.606	27.920	46.775	1.00	37.70
ATOM	1635	CZ	PHE	A	196	34.192	26.617	46.565	1.00	36.87
ATOM	1636	N	LYS	A	197	41.382	27.654	46.861	1.00	29.22
ATOM	1637	CA	LYS	A	197	42.794	28.014	46.666	1.00	28.21
ATOM	1638	C	LYS	A	197	43.696	26.804	46.447	1.00	28.32
ATOM	1639	O	LYS	A	197	44.608	26.849	45.628	1.00	27.69
ATOM	1640	CB	LYS	A	197	43.325	28.844	47.846	1.00	34.00
ATOM	1641	CG	LYS	A	197	42.631	30.211	47.978	1.00	39.87
ATOM	1642	CD	LYS	A	197	43.145	31.239	46.948	1.00	46.22
ATOM	1643	CE	LYS	A	197	42.217	32.474	46.852	1.00	51.05
ATOM	1644	NZ	LYS	A	197	42.007	32.935	45.439	1.00	52.01
ATOM	1645	N	VAL	A	198	43.478	25.723	47.193	1.00	22.40
ATOM	1646	CA	VAL	A	198	44.247	24.500	46.941	1.00	23.35
ATOM	1647	C	VAL	A	198	43.965	23.996	45.514	1.00	17.98
ATOM	1648	O	VAL	A	198	44.864	23.626	44.791	1.00	22.30
ATOM	1649	CB	VAL	A	198	43.920	23.386	47.985	1.00	24.72
ATOM	1650	CG1	VAL	A	198	44.705	22.142	47.699	1.00	23.99
ATOM	1651	CG2	VAL	A	198	44.216	23.864	49.419	1.00	26.35
ATOM	1652	N	ARG	A	199	42.702	24.005	45.113	1.00	20.52
ATOM	1653	CA	ARG	A	199	42.321	23.564	43.770	1.00	24.64
ATOM	1654	C	ARG	A	199	43.010	24.403	42.702	1.00	26.05
ATOM	1655	O	ARG	A	199	43.632	23.864	41.779	1.00	25.25
ATOM	1656	CB	ARG	A	199	40.820	23.671	43.573	1.00	21.92
ATOM	1657	CG	ARG	A	199	40.002	22.546	44.139	1.00	22.65
ATOM	1658	CD	ARG	A	199	38.543	22.750	43.832	1.00	24.05
ATOM	1659	NE	ARG	A	199	37.716	21.612	44.177	1.00	22.40
ATOM	1660	CZ	ARG	A	199	36.489	21.428	43.719	1.00	25.49
ATOM	1661	NH1	ARG	A	199	35.934	22.318	42.896	1.00	28.08
ATOM	1662	NH2	ARG	A	199	35.809	20.343	44.068	1.00	24.68
ATOM	1663	N	GLU	A	200	42.934	25.722	42.876	1.00	29.34
ATOM	1664	CA	GLU	A	200	43.434	26.682	41.892	1.00	33.45
ATOM	1665	C	GLU	A	200	44.917	26.519	41.649	1.00	32.84
ATOM	1666	O	GLU	A	200	45.398	26.834	40.574	1.00	36.40
ATOM	1667	CB	GLU	A	200	43.109	28.113	42.330	1.00	34.88
ATOM	1668	CG	GLU	A	200	41.639	28.441	42.163	1.00	39.29

ATOM	1669	CD	GLU	A	200	41.224	29.742	42.834	1.00 45.70
ATOM	1670	OE1	GLU	A	200	42.125	30.496	43.266	1.00 46.97
ATOM	1671	OE2	GLU	A	200	39.994	29.997	42.918	1.00 45.60
ATOM	1672	N	SER	A	201	45.616	25.972	42.642	1.00 32.36
ATOM	1673	CA	SER	A	201	47.037	25.742	42.573	1.00 26.44
ATOM	1674	C	SER	A	201	47.454	24.601	41.686	1.00 30.06
ATOM	1675	O	SER	A	201	48.628	24.493	41.358	1.00 32.56
ATOM	1676	CB	SER	A	201	47.575	25.487	43.985	1.00 31.12
ATOM	1677	OG	SER	A	201	47.425	24.135	44.415	1.00 28.72
ATOM	1678	N	GLY	A	202	46.533	23.709	41.331	1.00 30.71
ATOM	1679	CA	GLY	A	202	46.897	22.485	40.627	1.00 28.34
ATOM	1680	C	GLY	A	202	47.249	21.292	41.510	1.00 30.55
ATOM	1681	O	GLY	A	202	47.507	20.199	41.000	1.00 28.65
ATOM	1682	N	SER	A	203	47.244	21.482	42.828	1.00 30.37
ATOM	1683	CA	SER	A	203	47.741	20.460	43.763	1.00 29.05
ATOM	1684	C	SER	A	203	46.834	19.237	43.882	1.00 28.76
ATOM	1685	O	SER	A	203	47.301	18.176	44.310	1.00 31.80
ATOM	1686	CB	SER	A	203	47.947	21.049	45.163	1.00 29.41
ATOM	1687	OG	SER	A	203	49.010	21.988	45.207	1.00 29.86
ATOM	1688	N	LEU	A	204	45.548	19.389	43.557	1.00 28.79
ATOM	1689	CA	LEU	A	204	44.591	18.272	43.554	1.00 29.64
ATOM	1690	C	LEU	A	204	44.403	17.627	42.171	1.00 31.08
ATOM	1691	O	LEU	A	204	43.657	16.661	42.036	1.00 32.01
ATOM	1692	CB	LEU	A	204	43.233	18.740	44.066	1.00 29.85
ATOM	1693	CG	LEU	A	204	43.216	19.303	45.483	1.00 33.56
ATOM	1694	CD1	LEU	A	204	41.887	19.909	45.803	1.00 31.20
ATOM	1695	CD2	LEU	A	204	43.549	18.204	46.483	1.00 38.36
ATOM	1696	N	SER	A	205	45.076	18.168	41.158	1.00 29.37
ATOM	1697	CA	SER	A	205	44.866	17.798	39.772	1.00 28.36
ATOM	1698	C	SER	A	205	45.673	16.562	39.344	1.00 31.37
ATOM	1699	O	SER	A	205	46.700	16.258	39.949	1.00 31.75
ATOM	1700	CB	SER	A	205	45.189	18.986	38.871	1.00 30.29
ATOM	1701	OG	SER	A	205	44.411	20.111	39.263	1.00 34.52
ATOM	1702	N	PRO	A	206	45.191	15.856	38.307	1.00 34.16
ATOM	1703	CA	PRO	A	206	45.768	14.574	37.870	1.00 34.58
ATOM	1704	C	PRO	A	206	47.210	14.593	37.379	1.00 31.19
ATOM	1705	O	PRO	A	206	47.836	13.557	37.458	1.00 35.03
ATOM	1706	CB	PRO	A	206	44.843	14.146	36.701	1.00 36.26
ATOM	1707	CG	PRO	A	206	43.597	14.874	36.907	1.00 36.19
ATOM	1708	CD	PRO	A	206	44.003	16.205	37.496	1.00 34.78
ATOM	1709	N	GLU	A	207	47.716	15.717	36.896	1.00 33.37
ATOM	1710	CA	GLU	A	207	49.132	15.830	36.501	1.00 37.01
ATOM	1711	C	GLU	A	207	50.115	15.606	37.666	1.00 36.38
ATOM	1712	O	GLU	A	207	51.309	15.423	37.437	1.00 36.45
ATOM	1713	CB	GLU	A	207	49.449	17.205	35.886	1.00 40.05
ATOM	1714	CG	GLU	A	207	48.399	17.773	34.933	1.00 46.50
ATOM	1715	CD	GLU	A	207	47.438	18.725	35.629	1.00 52.97
ATOM	1716	OE1	GLU	A	207	47.805	19.912	35.885	1.00 59.90
ATOM	1717	OE2	GLU	A	207	46.320	18.275	35.939	1.00 50.42
ATOM	1718	N	HIS	A	208	49.643	15.656	38.911	1.00 33.01
ATOM	1719	CA	HIS	A	208	50.538	15.446	40.049	1.00 27.65
ATOM	1720	C	HIS	A	208	50.116	14.231	40.821	1.00 25.96
ATOM	1721	O	HIS	A	208	48.999	13.747	40.669	1.00 27.36
ATOM	1722	CB	HIS	A	208	50.536	16.695	40.941	1.00 26.63
ATOM	1723	CG	HIS	A	208	50.900	17.943	40.198	1.00 26.81
ATOM	1724	ND1	HIS	A	208	49.957	18.821	39.713	1.00 28.46
ATOM	1725	CD2	HIS	A	208	52.107	18.441	39.823	1.00 28.59
ATOM	1726	CE1	HIS	A	208	50.564	19.805	39.069	1.00 29.60

ATOM	1727	NE2	HIS	A	208	51.869	19.605	39.132	1.00 29.80
ATOM	1728	N	GLY	A	209	51.015	13.727	41.647	1.00 25.77
ATOM	1729	CA	GLY	A	209	50.648	12.757	42.652	1.00 25.91
ATOM	1730	C	GLY	A	209	49.670	13.353	43.646	1.00 25.50
ATOM	1731	O	GLY	A	209	49.354	14.552	43.614	1.00 26.79
ATOM	1732	N	PRO	A	210	49.134	12.501	44.502	1.00 25.06
ATOM	1733	CA	PRO	A	210	48.108	12.930	45.456	1.00 26.32
ATOM	1734	C	PRO	A	210	48.597	13.973	46.457	1.00 21.20
ATOM	1735	O	PRO	A	210	49.714	13.902	46.951	1.00 20.44
ATOM	1736	CB	PRO	A	210	47.710	11.632	46.187	1.00 24.37
ATOM	1737	CG	PRO	A	210	48.700	10.614	45.789	1.00 28.61
ATOM	1738	CD	PRO	A	210	49.418	11.061	44.574	1.00 27.20
ATOM	1739	N	VAL	A	211	47.740	14.942	46.719	1.00 23.27
ATOM	1740	CA	VAL	A	211	47.928	15.872	47.816	1.00 22.75
ATOM	1741	C	VAL	A	211	48.129	15.103	49.131	1.00 24.67
ATOM	1742	O	VAL	A	211	47.508	14.043	49.337	1.00 23.47
ATOM	1743	CB	VAL	A	211	46.725	16.840	47.866	1.00 23.08
ATOM	1744	CG1	VAL	A	211	45.451	16.164	48.401	1.00 25.62
ATOM	1745	CG2	VAL	A	211	47.064	18.080	48.646	1.00 29.23
ATOM	1746	N	VAL	A	212	49.011	15.612	49.994	1.00 20.82
ATOM	1747	CA	VAL	A	212	49.220	15.070	51.334	1.00 20.51
ATOM	1748	C	VAL	A	212	48.486	15.952	52.328	1.00 25.29
ATOM	1749	O	VAL	A	212	48.712	17.142	52.368	1.00 26.61
ATOM	1750	CB	VAL	A	212	50.699	14.957	51.691	1.00 21.70
ATOM	1751	CG1	VAL	A	212	50.893	14.460	53.118	1.00 23.78
ATOM	1752	CG2	VAL	A	212	51.388	14.002	50.748	1.00 21.34
ATOM	1753	N	VAL	A	213	47.585	15.356	53.107	1.00 22.18
ATOM	1754	CA	VAL	A	213	46.700	16.087	53.990	1.00 20.71
ATOM	1755	C	VAL	A	213	46.904	15.583	55.393	1.00 21.82
ATOM	1756	O	VAL	A	213	46.973	14.369	55.600	1.00 21.30
ATOM	1757	CB	VAL	A	213	45.214	15.855	53.618	1.00 18.46
ATOM	1758	CG1	VAL	A	213	44.314	16.704	54.468	1.00 17.92
ATOM	1759	CG2	VAL	A	213	44.961	16.130	52.136	1.00 18.57
ATOM	1760	N	HIS	A	214	47.009	16.499	56.360	1.00 21.27
ATOM	1761	CA	HIS	A	214	47.013	16.107	57.780	1.00 18.49
ATOM	1762	C	HIS	A	214	46.329	17.127	58.658	1.00 22.46
ATOM	1763	O	HIS	A	214	46.217	18.292	58.266	1.00 19.52
ATOM	1764	CB	HIS	A	214	48.424	15.861	58.255	1.00 22.66
ATOM	1765	CG	HIS	A	214	49.242	17.103	58.440	1.00 23.62
ATOM	1766	ND1	HIS	A	214	49.465	17.670	59.677	1.00 21.41
ATOM	1767	CD2	HIS	A	214	49.868	17.899	57.542	1.00 24.31
ATOM	1768	CE1	HIS	A	214	50.247	18.724	59.536	1.00 21.76
ATOM	1769	NE2	HIS	A	214	50.494	18.893	58.251	1.00 21.07
ATOM	1770	N	ACYS	A	215	45.982	16.650	59.851	0.50 21.29
ATOM	1771	CA	ACYS	A	215	45.553	17.584	60.885	0.50 21.43
ATOM	1772	C	ACYS	A	215	46.211	17.303	62.215	0.50 24.05
ATOM	1773	O	ACYS	A	215	47.355	16.913	62.307	0.50 22.32
ATOM	1774	CB	ACYS	A	215	44.037	17.520	61.166	0.50 22.73
ATOM	1775	SG	ACYS	A	215	43.916	18.029	62.855	0.50 30.96
ATOM	1776	N	BCYS	A	215	45.982	16.650	59.851	0.50 21.29
ATOM	1777	CA	BCYS	A	215	45.553	17.584	60.885	0.50 21.43
ATOM	1778	C	BCYS	A	215	46.211	17.303	62.215	0.50 24.05
ATOM	1779	O	BCYS	A	215	47.355	16.913	62.307	0.50 22.32
ATOM	1780	CB	BCYS	A	215	44.037	17.520	61.166	0.50 22.73
ATOM	1781	SG	BCYS	A	215	43.916	18.029	62.855	0.50 30.96
ATOM	1782	N	ASER	A	216	45.432	17.553	63.271	0.50 28.96
ATOM	1783	CA	ASER	A	216	45.887	17.111	64.593	0.50 33.95
ATOM	1784	C	ASER	A	216	45.405	15.709	64.892	0.50 38.49

ATOM	1785	O	ASER	A	216	44.329	15.318	64.490	0.50 38.68
ATOM	1786	CB	ASER	A	216	45.451	18.035	65.735	0.50 34.57
ATOM	1787	OG	ASER	A	216	45.116	19.351	65.362	0.50 36.62
ATOM	1788	N	BSER	A	216	45.432	17.553	63.271	0.50 28.96
ATOM	1789	CA	BSER	A	216	45.887	17.111	64.593	0.50 33.95
ATOM	1790	C	BSER	A	216	45.405	15.709	64.892	0.50 38.49
ATOM	1791	O	BSER	A	216	44.329	15.318	64.490	0.50 38.68
ATOM	1792	CB	BSER	A	216	45.451	18.035	65.735	0.50 34.57
ATOM	1793	OG	BSER	A	216	45.116	19.351	65.362	0.50 36.62
ATOM	1794	N	ALA	A	217	45.830	14.927	65.877	1.00 39.80
ATOM	1795	CA	ALA	A	217	45.628	13.542	66.296	1.00 39.86
ATOM	1796	C	ALA	A	217	44.166	13.315	66.672	1.00 39.03
ATOM	1797	O	ALA	A	217	43.627	14.011	67.529	1.00 36.63
ATOM	1798	CB	ALA	A	217	46.534	13.209	67.476	1.00 39.80
ATOM	1799	N	GLY	A	218	43.518	12.380	65.978	1.00 44.45
ATOM	1800	CA	GLY	A	218	42.248	11.824	66.419	1.00 44.76
ATOM	1801	C	GLY	A	218	41.011	12.697	66.321	1.00 48.15
ATOM	1802	O	GLY	A	218	39.953	12.245	66.742	1.00 50.53
ATOM	1803	N	ILE	A	219	41.106	13.918	65.777	1.00 47.19
ATOM	1804	CA	ILE	A	219	39.928	14.807	65.728	1.00 47.39
ATOM	1805	C	ILE	A	219	39.495	15.264	64.317	1.00 43.76
ATOM	1806	O	ILE	A	219	38.817	16.268	64.172	1.00 43.45
ATOM	1807	CB	ILE	A	219	40.050	16.012	66.745	1.00 50.42
ATOM	1808	CG1	ILE	A	219	40.920	17.169	66.222	1.00 51.81
ATOM	1809	CG2	ILE	A	219	40.529	15.526	68.118	1.00 49.25
ATOM	1810	CD1	ILE	A	219	42.192	16.787	65.649	1.00 52.65
ATOM	1811	N	GLY	A	220	39.883	14.508	63.291	1.00 43.30
ATOM	1812	CA	GLY	A	220	39.321	14.664	61.954	1.00 39.26
ATOM	1813	C	GLY	A	220	39.890	15.811	61.140	1.00 37.46
ATOM	1814	O	GLY	A	220	41.113	15.952	61.045	1.00 40.16
ATOM	1815	N	ARG	A	221	38.991	16.631	60.582	1.00 30.80
ATOM	1816	CA	ARG	A	221	39.298	17.738	59.668	1.00 29.00
ATOM	1817	C	ARG	A	221	39.765	17.340	58.251	1.00 24.28
ATOM	1818	O	ARG	A	221	39.248	17.862	57.274	1.00 24.99
ATOM	1819	CB	ARG	A	221	40.301	18.743	60.277	1.00 31.09
ATOM	1820	CG	ARG	A	221	39.907	19.330	61.619	1.00 28.54
ATOM	1821	CD	ARG	A	221	40.937	20.316	62.157	1.00 26.55
ATOM	1822	NE	ARG	A	221	40.869	20.481	63.600	1.00 25.85
ATOM	1823	CZ	ARG	A	221	41.695	21.278	64.294	1.00 28.63
ATOM	1824	NH1	ARG	A	221	42.662	21.955	63.686	1.00 23.62
ATOM	1825	NH2	ARG	A	221	41.558	21.385	65.604	1.00 27.34
ATOM	1826	N	SER	A	222	40.767	16.476	58.156	1.00 24.21
ATOM	1827	CA	SER	A	222	41.286	15.989	56.887	1.00 26.35
ATOM	1828	C	SER	A	222	40.179	15.345	56.042	1.00 27.07
ATOM	1829	O	SER	A	222	40.097	15.574	54.838	1.00 26.61
ATOM	1830	CB	SER	A	222	42.397	14.972	57.125	1.00 24.83
ATOM	1831	OG	SER	A	222	43.374	15.456	58.013	1.00 27.62
ATOM	1832	N	GLY	A	223	39.323	14.560	56.693	1.00 25.96
ATOM	1833	CA	GLY	A	223	38.229	13.895	56.029	1.00 26.22
ATOM	1834	C	GLY	A	223	37.211	14.872	55.489	1.00 27.52
ATOM	1835	O	GLY	A	223	36.677	14.671	54.407	1.00 29.73
ATOM	1836	N	THR	A	224	36.952	15.934	56.239	1.00 27.07
ATOM	1837	CA	THR	A	224	36.051	16.987	55.800	1.00 26.92
ATOM	1838	C	THR	A	224	36.540	17.673	54.532	1.00 23.15
ATOM	1839	O	THR	A	224	35.758	17.901	53.621	1.00 23.86
ATOM	1840	CB	THR	A	224	35.887	18.013	56.927	1.00 31.61
ATOM	1841	OG1	THR	A	224	35.214	17.394	58.031	1.00 31.13
ATOM	1842	CG2	THR	A	224	34.975	19.146	56.522	1.00 34.93

ATOM	1843	N	PHE	A	225	37.828	18.009	54.486	1.00 23.12
ATOM	1844	CA	PHE	A	225	38.448	18.612	53.315	1.00 22.32
ATOM	1845	C	PHE	A	225	38.251	17.747	52.060	1.00 24.02
ATOM	1846	O	PHE	A	225	37.782	18.238	51.027	1.00 23.24
ATOM	1847	CB	PHE	A	225	39.948	18.816	53.557	1.00 22.48
ATOM	1848	CG	PHE	A	225	40.664	19.484	52.414	1.00 22.57
ATOM	1849	CD1	PHE	A	225	41.323	18.732	51.449	1.00 22.46
ATOM	1850	CD2	PHE	A	225	40.673	20.865	52.300	1.00 25.95
ATOM	1851	CE1	PHE	A	225	41.993	19.347	50.404	1.00 24.23
ATOM	1852	CE2	PHE	A	225	41.349	21.490	51.248	1.00 23.96
ATOM	1853	CZ	PHE	A	225	42.003	20.738	50.308	1.00 23.02
ATOM	1854	N	CYS	A	226	38.599	16.468	52.161	1.00 22.58
ATOM	1855	CA	CYS	A	226	38.488	15.528	51.028	1.00 24.24
ATOM	1856	C	CYS	A	226	37.036	15.217	50.638	1.00 25.48
ATOM	1857	O	CYS	A	226	36.689	15.170	49.452	1.00 24.77
ATOM	1858	CB	CYS	A	226	39.243	14.232	51.338	1.00 24.74
ATOM	1859	SG	CYS	A	226	40.990	14.548	51.722	1.00 26.51
ATOM	1860	N	LEU	A	227	36.191	15.025	51.635	1.00 25.13
ATOM	1861	CA	LEU	A	227	34.780	14.744	51.409	1.00 26.81
ATOM	1862	C	LEU	A	227	34.098	15.862	50.643	1.00 26.57
ATOM	1863	O	LEU	A	227	33.355	15.623	49.693	1.00 28.06
ATOM	1864	CB	LEU	A	227	34.055	14.572	52.741	1.00 28.52
ATOM	1865	CG	LEU	A	227	32.563	14.216	52.682	1.00 27.60
ATOM	1866	CD1	LEU	A	227	32.319	12.963	51.831	1.00 26.20
ATOM	1867	CD2	LEU	A	227	32.017	14.037	54.086	1.00 30.02
ATOM	1868	N	ALA	A	228	34.340	17.082	51.086	1.00 24.59
ATOM	1869	CA	ALA	A	228	33.752	18.262	50.465	1.00 25.53
ATOM	1870	C	ALA	A	228	34.244	18.410	49.041	1.00 24.66
ATOM	1871	O	ALA	A	228	33.460	18.678	48.136	1.00 26.93
ATOM	1872	CB	ALA	A	228	34.104	19.502	51.267	1.00 24.92
ATOM	1873	N	ASP	A	229	35.548	18.200	48.848	1.00 21.07
ATOM	1874	CA	ASP	A	229	36.158	18.294	47.535	1.00 21.55
ATOM	1875	C	ASP	A	229	35.554	17.307	46.529	1.00 24.44
ATOM	1876	O	ASP	A	229	35.207	17.677	45.400	1.00 23.83
ATOM	1877	CB	ASP	A	229	37.650	18.058	47.655	1.00 21.03
ATOM	1878	CG	ASP	A	229	38.359	18.170	46.342	1.00 24.70
ATOM	1879	OD1	ASP	A	229	38.129	19.175	45.649	1.00 22.45
ATOM	1880	OD2	ASP	A	229	39.145	17.295	45.910	1.00 24.46
ATOM	1881	N	THR	A	230	35.473	16.051	46.939	1.00 22.53
ATOM	1882	CA	THR	A	230	34.986	14.979	46.095	1.00 26.13
ATOM	1883	C	THR	A	230	33.515	15.178	45.771	1.00 26.21
ATOM	1884	O	THR	A	230	33.144	15.076	44.615	1.00 27.32
ATOM	1885	CB	THR	A	230	35.234	13.602	46.762	1.00 25.54
ATOM	1886	OG1	THR	A	230	36.600	13.243	46.572	1.00 23.46
ATOM	1887	CG2	THR	A	230	34.455	12.461	46.073	1.00 28.27
ATOM	1888	N	CYS	A	231	32.699	15.472	46.782	1.00 26.34
ATOM	1889	CA	CYS	A	231	31.268	15.706	46.593	1.00 28.13
ATOM	1890	C	CYS	A	231	31.019	16.827	45.591	1.00 27.64
ATOM	1891	O	CYS	A	231	30.196	16.693	44.706	1.00 31.51
ATOM	1892	CB	CYS	A	231	30.573	16.046	47.926	1.00 30.75
ATOM	1893	SG	CYS	A	231	30.324	14.640	49.046	1.00 31.45
ATOM	1894	N	LEU	A	232	31.745	17.926	45.713	1.00 27.97
ATOM	1895	CA	LEU	A	232	31.550	19.047	44.794	1.00 28.23
ATOM	1896	C	LEU	A	232	31.942	18.679	43.369	1.00 29.48
ATOM	1897	O	LEU	A	232	31.265	19.052	42.401	1.00 26.16
ATOM	1898	CB	LEU	A	232	32.331	20.254	45.260	1.00 27.13
ATOM	1899	CG	LEU	A	232	31.816	20.889	46.547	1.00 28.98
ATOM	1900	CD1	LEU	A	232	32.805	21.934	47.040	1.00 28.37

ATOM	1901	CD2	LEU	A	232	30.443	21.492	46.345	1.00 32.86
ATOM	1902	N	LEU	A	233	33.019	17.914	43.254	1.00 27.18
ATOM	1903	CA	LEU	A	233	33.473	17.442	41.957	1.00 28.48
ATOM	1904	C	LEU	A	233	32.429	16.527	41.298	1.00 29.51
ATOM	1905	O	LEU	A	233	32.143	16.664	40.110	1.00 27.14
ATOM	1906	CB	LEU	A	233	34.809	16.741	42.110	1.00 30.57
ATOM	1907	CG	LEU	A	233	35.788	16.847	40.964	1.00 35.34
ATOM	1908	CD1	LEU	A	233	36.159	18.310	40.635	1.00 39.45
ATOM	1909	CD2	LEU	A	233	37.003	16.021	41.327	1.00 39.50
ATOM	1910	N	LEU	A	234	31.830	15.630	42.077	1.00 26.58
ATOM	1911	CA	LEU	A	234	30.833	14.711	41.555	1.00 29.13
ATOM	1912	C	LEU	A	234	29.574	15.443	41.127	1.00 29.39
ATOM	1913	O	LEU	A	234	28.915	15.025	40.190	1.00 29.61
ATOM	1914	CB	LEU	A	234	30.463	13.643	42.589	1.00 28.81
ATOM	1915	CG	LEU	A	234	31.527	12.619	42.998	1.00 29.20
ATOM	1916	CD1	LEU	A	234	31.822	11.669	41.849	1.00 32.34
ATOM	1917	CD2	LEU	A	234	31.057	11.839	44.210	1.00 26.85
ATOM	1918	N	MET	A	235	29.227	16.522	41.826	1.00 33.19
ATOM	1919	CA	MET	A	235	28.057	17.314	41.464	1.00 33.17
ATOM	1920	C	MET	A	235	28.224	17.968	40.088	1.00 34.16
ATOM	1921	O	MET	A	235	27.267	18.060	39.335	1.00 37.58
ATOM	1922	CB	MET	A	235	27.752	18.354	42.533	1.00 33.08
ATOM	1923	CG	MET	A	235	27.218	17.733	43.794	1.00 37.93
ATOM	1924	SD	MET	A	235	26.992	18.903	45.116	1.00 38.83
ATOM	1925	CE	MET	A	235	26.505	17.871	46.353	1.00 40.67
ATOM	1926	N	ASP	A	236	29.443	18.378	39.760	1.00 34.42
ATOM	1927	CA	ASP	A	236	29.801	18.860	38.424	1.00 35.78
ATOM	1928	C	ASP	A	236	29.906	17.793	37.323	1.00 37.28
ATOM	1929	O	ASP	A	236	29.743	18.119	36.154	1.00 36.30
ATOM	1930	CB	ASP	A	236	31.166	19.551	38.467	1.00 40.86
ATOM	1931	CG	ASP	A	236	31.060	21.045	38.568	1.00 45.84
ATOM	1932	OD1	ASP	A	236	30.172	21.666	37.909	1.00 49.22
ATOM	1933	OD2	ASP	A	236	31.855	21.681	39.276	1.00 49.02
ATOM	1934	N	LYS	A	237	30.232	16.553	37.686	1.00 36.32
ATOM	1935	CA	LYS	A	237	30.475	15.475	36.723	1.00 35.45
ATOM	1936	C	LYS	A	237	29.181	14.789	36.283	1.00 33.73
ATOM	1937	O	LYS	A	237	28.992	14.476	35.105	1.00 28.67
ATOM	1938	CB	LYS	A	237	31.404	14.422	37.347	1.00 36.84
ATOM	1939	CG	LYS	A	237	32.262	13.614	36.365	1.00 41.35
ATOM	1940	CD	LYS	A	237	33.411	12.887	37.086	1.00 41.67
ATOM	1941	CE	LYS	A	237	34.476	12.316	36.122	1.00 47.97
ATOM	1942	NZ	LYS	A	237	35.847	13.013	36.172	1.00 45.85
ATOM	1943	N	ARG	A	238	28.299	14.534	37.237	1.00 32.18
ATOM	1944	CA	ARG	A	238	27.157	13.655	36.993	1.00 34.57
ATOM	1945	C	ARG	A	238	26.034	14.365	36.262	1.00 35.08
ATOM	1946	O	ARG	A	238	25.798	15.562	36.470	1.00 32.96
ATOM	1947	CB	ARG	A	238	26.584	13.143	38.303	1.00 35.62
ATOM	1948	CG	ARG	A	238	27.366	12.041	38.912	1.00 33.98
ATOM	1949	CD	ARG	A	238	26.764	11.583	40.190	1.00 32.14
ATOM	1950	NE	ARG	A	238	27.503	10.469	40.780	1.00 29.90
ATOM	1951	CZ	ARG	A	238	27.108	9.846	41.875	1.00 31.16
ATOM	1952	NH1	ARG	A	238	26.009	10.228	42.496	1.00 36.13
ATOM	1953	NH2	ARG	A	238	27.833	8.857	42.383	1.00 37.35
ATOM	1954	N	LYS	A	239	25.327	13.587	35.452	1.00 34.64
ATOM	1955	CA	LYS	A	239	24.099	14.019	34.795	1.00 37.99
ATOM	1956	C	LYS	A	239	23.025	14.391	35.810	1.00 37.55
ATOM	1957	O	LYS	A	239	22.217	15.277	35.558	1.00 35.27
ATOM	1958	CB	LYS	A	239	23.591	12.917	33.857	1.00 39.88

ATOM	1959	CG	LYS	A	239	24.489	12.698	32.626	1.00 45.02
ATOM	1960	CD	LYS	A	239	24.059	11.472	31.773	1.00 52.00
ATOM	1961	CE	LYS	A	239	23.645	11.832	30.330	1.00 54.36
ATOM	1962	NZ	LYS	A	239	24.672	11.399	29.329	1.00 57.23
ATOM	1963	N	ASP	A	240	23.042	13.721	36.962	1.00 39.09
ATOM	1964	CA	ASP	A	240	22.107	13.970	38.057	1.00 39.45
ATOM	1965	C	ASP	A	240	22.853	14.406	39.351	1.00 36.92
ATOM	1966	O	ASP	A	240	23.147	13.578	40.211	1.00 38.63
ATOM	1967	CB	ASP	A	240	21.308	12.688	38.291	1.00 39.46
ATOM	1968	CG	ASP	A	240	20.200	12.847	39.313	1.00 39.85
ATOM	1969	OD1	ASP	A	240	19.876	13.993	39.740	1.00 38.51
ATOM	1970	OD2	ASP	A	240	19.594	11.843	39.742	1.00 42.08
ATOM	1971	N	PRO	A	241	23.176	15.690	39.479	1.00 36.36
ATOM	1972	CA	PRO	A	241	23.862	16.215	40.674	1.00 37.38
ATOM	1973	C	PRO	A	241	23.215	15.841	42.022	1.00 39.56
ATOM	1974	O	PRO	A	241	23.926	15.723	43.021	1.00 39.31
ATOM	1975	CB	PRO	A	241	23.785	17.740	40.492	1.00 37.29
ATOM	1976	CG	PRO	A	241	23.527	17.971	39.061	1.00 37.23
ATOM	1977	CD	PRO	A	241	22.932	16.735	38.475	1.00 37.85
ATOM	1978	N	SER	A	242	21.893	15.666	42.043	1.00 38.69
ATOM	1979	CA	SER	A	242	21.138	15.431	43.282	1.00 37.48
ATOM	1980	C	SER	A	242	21.262	14.001	43.772	1.00 35.92
ATOM	1981	O	SER	A	242	20.826	13.694	44.868	1.00 36.57
ATOM	1982	CB	SER	A	242	19.652	15.764	43.066	1.00 41.14
ATOM	1983	OG	SER	A	242	18.980	14.695	42.410	1.00 43.22
ATOM	1984	N	SER	A	243	21.821	13.121	42.943	1.00 34.07
ATOM	1985	CA	SER	A	243	22.116	11.752	43.336	1.00 37.77
ATOM	1986	C	SER	A	243	23.381	11.645	44.197	1.00 36.66
ATOM	1987	O	SER	A	243	23.640	10.589	44.763	1.00 40.77
ATOM	1988	CB	SER	A	243	22.270	10.852	42.096	1.00 38.01
ATOM	1989	OG	SER	A	243	23.450	11.164	41.363	1.00 40.41
ATOM	1990	N	VAL	A	244	24.172	12.717	44.266	1.00 37.13
ATOM	1991	CA	VAL	A	244	25.385	12.747	45.092	1.00 36.10
ATOM	1992	C	VAL	A	244	24.947	12.748	46.556	1.00 35.80
ATOM	1993	O	VAL	A	244	24.359	13.718	47.049	1.00 32.02
ATOM	1994	CB	VAL	A	244	26.303	13.972	44.773	1.00 36.81
ATOM	1995	CG1	VAL	A	244	27.495	14.047	45.735	1.00 39.14
ATOM	1996	CG2	VAL	A	244	26.804	13.911	43.319	1.00 35.55
ATOM	1997	N	ASP	A	245	25.225	11.630	47.220	1.00 36.84
ATOM	1998	CA	ASP	A	245	24.843	11.383	48.608	1.00 37.92
ATOM	1999	C	ASP	A	245	26.101	11.444	49.471	1.00 34.42
ATOM	2000	O	ASP	A	245	26.954	10.564	49.395	1.00 36.20
ATOM	2001	CB	ASP	A	245	24.190	10.000	48.692	1.00 40.11
ATOM	2002	CG	ASP	A	245	23.606	9.684	50.071	1.00 43.89
ATOM	2003	OD1	ASP	A	245	23.995	10.292	51.104	1.00 46.19
ATOM	2004	OD2	ASP	A	245	22.732	8.815	50.194	1.00 48.65
ATOM	2005	N	ILE	A	246	26.226	12.496	50.268	1.00 34.58
ATOM	2006	CA	ILE	A	246	27.421	12.712	51.100	1.00 34.24
ATOM	2007	C	ILE	A	246	27.746	11.547	52.049	1.00 34.35
ATOM	2008	O	ILE	A	246	28.913	11.284	52.334	1.00 34.47
ATOM	2009	CB	ILE	A	246	27.297	14.049	51.866	1.00 36.01
ATOM	2010	CG1	ILE	A	246	28.607	14.400	52.578	1.00 38.62
ATOM	2011	CG2	ILE	A	246	26.156	14.011	52.868	1.00 40.14
ATOM	2012	CD1	ILE	A	246	28.676	15.858	53.015	1.00 41.03
ATOM	2013	N	LYS	A	247	26.717	10.836	52.502	1.00 33.97
ATOM	2014	CA	LYS	A	247	26.883	9.675	53.372	1.00 35.91
ATOM	2015	C	LYS	A	247	27.561	8.541	52.618	1.00 34.60
ATOM	2016	O	LYS	A	247	28.478	7.899	53.130	1.00 33.85

ATOM	2017	CB	LYS	A	247	25.533	9.210	53.949	1.00 37.68
ATOM	2018	CG	LYS	A	247	24.698	10.317	54.636	1.00 41.97
ATOM	2019	CD	LYS	A	247	23.300	9.831	55.115	1.00 45.11
ATOM	2020	CE	LYS	A	247	22.342	9.488	53.965	1.00 45.33
ATOM	2021	NZ	LYS	A	247	21.941	10.653	53.150	1.00 44.37
ATOM	2022	N	LYS	A	248	27.119	8.316	51.386	1.00 37.62
ATOM	2023	CA	LYS	A	248	27.696	7.291	50.525	1.00 37.40
ATOM	2024	C	LYS	A	248	29.133	7.619	50.101	1.00 34.78
ATOM	2025	O	LYS	A	248	29.984	6.725	50.010	1.00 32.91
ATOM	2026	CB	LYS	A	248	26.803	7.072	49.300	1.00 41.83
ATOM	2027	CG	LYS	A	248	25.439	6.441	49.645	1.00 47.35
ATOM	2028	CD	LYS	A	248	24.879	5.571	48.509	1.00 51.20
ATOM	2029	CE	LYS	A	248	23.390	5.239	48.712	1.00 52.76
ATOM	2030	NZ	LYS	A	248	22.490	6.336	48.233	1.00 51.45
ATOM	2031	N	VAL	A	249	29.413	8.900	49.859	1.00 34.70
ATOM	2032	CA	VAL	A	249	30.768	9.315	49.505	1.00 30.71
ATOM	2033	C	VAL	A	249	31.673	9.130	50.714	1.00 28.52
ATOM	2034	O	VAL	A	249	32.768	8.614	50.582	1.00 24.38
ATOM	2035	CB	VAL	A	249	30.832	10.768	48.997	1.00 28.72
ATOM	2036	CG1	VAL	A	249	32.284	11.191	48.743	1.00 32.77
ATOM	2037	CG2	VAL	A	249	30.040	10.918	47.729	1.00 30.80
ATOM	2038	N	LEU	A	250	31.203	9.546	51.889	1.00 28.31
ATOM	2039	CA	LEU	A	250	31.950	9.355	53.128	1.00 30.22
ATOM	2040	C	LEU	A	250	32.248	7.869	53.379	1.00 29.53
ATOM	2041	O	LEU	A	250	33.384	7.502	53.691	1.00 28.46
ATOM	2042	CB	LEU	A	250	31.195	9.940	54.324	1.00 30.09
ATOM	2043	CG	LEU	A	250	31.816	9.700	55.715	1.00 31.42
ATOM	2044	CD1	LEU	A	250	33.252	10.149	55.775	1.00 31.57
ATOM	2045	CD2	LEU	A	250	31.025	10.411	56.795	1.00 30.92
ATOM	2046	N	LEU	A	251	31.243	7.018	53.206	1.00 30.43
ATOM	2047	CA	LEU	A	251	31.421	5.583	53.441	1.00 31.75
ATOM	2048	C	LEU	A	251	32.414	5.003	52.479	1.00 28.77
ATOM	2049	O	LEU	A	251	33.220	4.167	52.861	1.00 27.12
ATOM	2050	CB	LEU	A	251	30.100	4.825	53.353	1.00 35.92
ATOM	2051	CG	LEU	A	251	29.236	4.875	54.618	1.00 39.34
ATOM	2052	CD1	LEU	A	251	27.823	4.403	54.280	1.00 43.05
ATOM	2053	CD2	LEU	A	251	29.846	4.037	55.743	1.00 38.51
ATOM	2054	N	GLU	A	252	32.411	5.477	51.237	1.00 29.11
ATOM	2055	CA	GLU	A	252	33.403	5.015	50.258	1.00 27.20
ATOM	2056	C	GLU	A	252	34.828	5.444	50.641	1.00 30.00
ATOM	2057	O	GLU	A	252	35.787	4.689	50.516	1.00 31.16
ATOM	2058	CB	GLU	A	252	33.035	5.548	48.882	1.00 32.72
ATOM	2059	CG	GLU	A	252	34.048	5.232	47.792	1.00 35.50
ATOM	2060	CD	GLU	A	252	34.041	3.768	47.382	1.00 40.85
ATOM	2061	OE1	GLU	A	252	33.055	3.059	47.707	1.00 37.49
ATOM	2062	OE2	GLU	A	252	35.020	3.343	46.719	1.00 39.81
ATOM	2063	N	MET	A	253	34.961	6.682	51.099	1.00 30.83
ATOM	2064	CA	MET	A	253	36.247	7.219	51.533	1.00 30.96
ATOM	2065	C	MET	A	253	36.742	6.424	52.736	1.00 28.97
ATOM	2066	O	MET	A	253	37.912	6.091	52.851	1.00 28.87
ATOM	2067	CB	MET	A	253	36.065	8.691	51.930	1.00 29.25
ATOM	2068	CG	MET	A	253	37.065	9.640	51.346	1.00 35.75
ATOM	2069	SD	MET	A	253	36.473	11.363	51.342	1.00 34.89
ATOM	2070	CE	MET	A	253	36.648	11.727	49.596	1.00 33.07
ATOM	2071	N	ARG	A	254	35.807	6.136	53.629	1.00 30.28
ATOM	2072	CA	ARG	A	254	36.061	5.427	54.875	1.00 32.59
ATOM	2073	C	ARG	A	254	36.654	4.013	54.659	1.00 32.55
ATOM	2074	O	ARG	A	254	37.296	3.460	55.542	1.00 30.27

ATOM	2075	CB	ARG	A	254	34.745	5.422	55.652	1.00 38.30
ATOM	2076	CG	ARG	A	254	34.776	4.884	57.034	1.00 45.57
ATOM	2077	CD	ARG	A	254	35.742	5.588	57.979	1.00 50.87
ATOM	2078	NE	ARG	A	254	35.742	4.925	59.277	1.00 49.69
ATOM	2079	CZ	ARG	A	254	36.213	3.707	59.497	1.00 48.16
ATOM	2080	NH1	ARG	A	254	36.156	3.199	60.719	1.00 52.85
ATOM	2081	NH2	ARG	A	254	36.750	2.993	58.516	1.00 47.70
ATOM	2082	N	LYS	A	255	36.511	3.458	53.458	1.00 29.98
ATOM	2083	CA	LYS	A	255	37.164	2.192	53.128	1.00 29.31
ATOM	2084	C	LYS	A	255	38.700	2.267	53.131	1.00 31.32
ATOM	2085	O	LYS	A	255	39.363	1.226	53.227	1.00 31.34
ATOM	2086	CB	LYS	A	255	36.712	1.716	51.734	1.00 30.37
ATOM	2087	CG	LYS	A	255	35.222	1.384	51.608	1.00 26.24
ATOM	2088	CD	LYS	A	255	34.791	1.347	50.151	1.00 26.82
ATOM	2089	CE	LYS	A	255	33.323	0.845	49.937	1.00 27.52
ATOM	2090	NZ	LYS	A	255	33.067	0.534	48.456	1.00 24.46
ATOM	2091	N	PHE	A	256	39.253	3.481	52.964	1.00 27.58
ATOM	2092	CA	PHE	A	256	40.690	3.693	52.796	1.00 25.60
ATOM	2093	C	PHE	A	256	41.392	4.191	54.054	1.00 23.14
ATOM	2094	O	PHE	A	256	42.600	4.017	54.221	1.00 25.79
ATOM	2095	CB	PHE	A	256	40.938	4.656	51.634	1.00 28.49
ATOM	2096	CG	PHE	A	256	40.416	4.151	50.301	1.00 25.93
ATOM	2097	CD1	PHE	A	256	41.181	3.311	49.516	1.00 28.34
ATOM	2098	CD2	PHE	A	256	39.152	4.503	49.857	1.00 25.47
ATOM	2099	CE1	PHE	A	256	40.702	2.846	48.288	1.00 28.01
ATOM	2100	CE2	PHE	A	256	38.677	4.044	48.649	1.00 23.45
ATOM	2101	CZ	PHE	A	256	39.452	3.211	47.865	1.00 25.89
ATOM	2102	N	ARG	A	257	40.649	4.847	54.928	1.00 24.88
ATOM	2103	CA	ARG	A	257	41.203	5.234	56.199	1.00 26.69
ATOM	2104	C	ARG	A	257	40.084	5.522	57.173	1.00 27.56
ATOM	2105	O	ARG	A	257	39.029	6.033	56.797	1.00 29.01
ATOM	2106	CB	ARG	A	257	42.120	6.461	56.045	1.00 26.90
ATOM	2107	CG	ARG	A	257	42.932	6.827	57.294	1.00 28.05
ATOM	2108	CD	ARG	A	257	43.883	8.013	57.024	1.00 26.37
ATOM	2109	NE	ARG	A	257	44.621	8.479	58.194	1.00 19.25
ATOM	2110	CZ	ARG	A	257	45.812	8.058	58.607	1.00 23.43
ATOM	2111	NH1	ARG	A	257	46.448	7.059	58.019	1.00 22.28
ATOM	2112	NH2	ARG	A	257	46.361	8.639	59.663	1.00 28.19
ATOM	2113	N	MET	A	258	40.352	5.204	58.433	1.00 29.28
ATOM	2114	CA	MET	A	258	39.426	5.426	59.535	1.00 33.32
ATOM	2115	C	MET	A	258	39.523	6.871	60.069	1.00 33.40
ATOM	2116	O	MET	A	258	40.485	7.575	59.789	1.00 24.99
ATOM	2117	CB	MET	A	258	39.711	4.399	60.656	1.00 36.62
ATOM	2118	CG	MET	A	258	41.087	4.534	61.324	1.00 43.85
ATOM	2119	SD	MET	A	258	41.460	3.404	62.774	1.00 51.60
ATOM	2120	CE	MET	A	258	42.050	1.920	61.953	1.00 45.75
ATOM	2121	N	GLY	A	259	38.513	7.300	60.814	1.00 32.82
ATOM	2122	CA	GLY	A	259	38.548	8.586	61.494	1.00 36.92
ATOM	2123	C	GLY	A	259	38.456	9.798	60.576	1.00 38.56
ATOM	2124	O	GLY	A	259	39.091	10.842	60.820	1.00 35.70
ATOM	2125	N	LEU	A	260	37.679	9.656	59.509	1.00 34.91
ATOM	2126	CA	LEU	A	260	37.484	10.742	58.571	1.00 35.45
ATOM	2127	C	LEU	A	260	36.578	11.823	59.155	1.00 36.54
ATOM	2128	O	LEU	A	260	36.900	13.010	59.087	1.00 37.25
ATOM	2129	CB	LEU	A	260	36.923	10.201	57.266	1.00 33.19
ATOM	2130	CG	LEU	A	260	37.904	9.287	56.528	1.00 33.16
ATOM	2131	CD1	LEU	A	260	37.319	8.911	55.197	1.00 35.18
ATOM	2132	CD2	LEU	A	260	39.285	9.907	56.353	1.00 34.68

ATOM	2133	N	ILE	A	261	35.452	11.418	59.724	1.00 37.56
ATOM	2134	CA	ILE	A	261	34.574	12.345	60.429	1.00 40.12
ATOM	2135	C	ILE	A	261	34.443	11.802	61.846	1.00 42.88
ATOM	2136	O	ILE	A	261	33.956	10.685	62.034	1.00 42.56
ATOM	2137	CB	ILE	A	261	33.195	12.447	59.730	1.00 41.51
ATOM	2138	CG1	ILE	A	261	33.358	12.831	58.255	1.00 44.63
ATOM	2139	CG2	ILE	A	261	32.290	13.474	60.423	1.00 41.66
ATOM	2140	CD1	ILE	A	261	33.854	14.256	58.003	1.00 45.20
ATOM	2141	N	GLN	A	262	34.904	12.582	62.822	1.00 44.63
ATOM	2142	CA	GLN	A	262	35.013	12.132	64.213	1.00 46.99
ATOM	2143	C	GLN	A	262	33.830	12.505	65.113	1.00 47.40
ATOM	2144	O	GLN	A	262	33.650	11.900	66.164	1.00 49.81
ATOM	2145	CB	GLN	A	262	36.305	12.674	64.851	1.00 46.30
ATOM	2146	CG	GLN	A	262	37.565	11.989	64.392	1.00 48.97
ATOM	2147	CD	GLN	A	262	37.666	10.520	64.830	1.00 51.67
ATOM	2148	OE1	GLN	A	262	36.752	9.738	64.612	1.00 59.14
ATOM	2149	NE2	GLN	A	262	38.794	10.148	65.416	1.00 56.82
ATOM	2150	N	THR	A	263	33.049	13.512	64.736	1.00 48.72
ATOM	2151	CA	THR	A	263	31.879	13.894	65.526	1.00 48.51
ATOM	2152	C	THR	A	263	30.688	14.228	64.645	1.00 49.93
ATOM	2153	O	THR	A	263	30.832	14.483	63.445	1.00 46.32
ATOM	2154	CB	THR	A	263	32.190	15.105	66.405	1.00 49.79
ATOM	2155	OG1	THR	A	263	32.603	16.202	65.587	1.00 48.64
ATOM	2156	CG2	THR	A	263	33.388	14.852	67.325	1.00 50.03
ATOM	2157	N	ALA	A	264	29.512	14.218	65.269	1.00 48.46
ATOM	2158	CA	ALA	A	264	28.264	14.619	64.635	1.00 48.90
ATOM	2159	C	ALA	A	264	28.331	16.034	64.080	1.00 47.97
ATOM	2160	O	ALA	A	264	27.724	16.307	63.051	1.00 46.14
ATOM	2161	CB	ALA	A	264	27.096	14.514	65.637	1.00 50.13
ATOM	2162	N	ASP	A	265	29.054	16.922	64.764	1.00 46.13
ATOM	2163	CA	ASP	A	265	29.173	18.312	64.341	1.00 49.36
ATOM	2164	C	ASP	A	265	30.000	18.452	63.072	1.00 46.31
ATOM	2165	O	ASP	A	265	29.739	19.329	62.261	1.00 47.97
ATOM	2166	CB	ASP	A	265	29.832	19.163	65.427	1.00 53.22
ATOM	2167	CG	ASP	A	265	28.992	19.277	66.681	1.00 61.01
ATOM	2168	OD1	ASP	A	265	27.747	19.406	66.572	1.00 68.83
ATOM	2169	OD2	ASP	A	265	29.505	19.259	67.827	1.00 65.34
ATOM	2170	N	GLN	A	266	31.027	17.623	62.938	1.00 42.43
ATOM	2171	CA	GLN	A	266	31.876	17.634	61.755	1.00 41.84
ATOM	2172	C	GLN	A	266	31.103	17.162	60.543	1.00 39.69
ATOM	2173	O	GLN	A	266	31.287	17.675	59.461	1.00 39.79
ATOM	2174	CB	GLN	A	266	33.084	16.722	61.942	1.00 42.22
ATOM	2175	CG	GLN	A	266	34.123	17.234	62.905	1.00 42.76
ATOM	2176	CD	GLN	A	266	35.476	16.563	62.702	1.00 45.93
ATOM	2177	OE1	GLN	A	266	35.558	15.387	62.298	1.00 42.79
ATOM	2178	NE2	GLN	A	266	36.541	17.310	62.974	1.00 43.52
ATOM	2179	N	LEU	A	267	30.255	16.160	60.737	1.00 40.23
ATOM	2180	CA	LEU	A	267	29.353	15.704	59.695	1.00 41.23
ATOM	2181	C	LEU	A	267	28.433	16.830	59.275	1.00 40.80
ATOM	2182	O	LEU	A	267	28.297	17.117	58.097	1.00 38.81
ATOM	2183	CB	LEU	A	267	28.520	14.537	60.193	1.00 41.88
ATOM	2184	CG	LEU	A	267	27.542	13.904	59.208	1.00 42.25
ATOM	2185	CD1	LEU	A	267	28.282	13.277	58.039	1.00 41.79
ATOM	2186	CD2	LEU	A	267	26.695	12.866	59.939	1.00 43.40
ATOM	2187	N	ARG	A	268	27.813	17.481	60.250	1.00 43.33
ATOM	2188	CA	ARG	A	268	26.912	18.585	59.957	1.00 42.44
ATOM	2189	C	ARG	A	268	27.662	19.638	59.152	1.00 39.47
ATOM	2190	O	ARG	A	268	27.170	20.110	58.136	1.00 36.25

ATOM	2191	CB	ARG	A	268	26.339	19.199	61.245	1.00	44.59
ATOM	2192	CG	ARG	A	268	25.365	20.357	60.992	1.00	47.22
ATOM	2193	CD	ARG	A	268	24.719	20.937	62.253	1.00	51.04
ATOM	2194	NE	ARG	A	268	23.755	21.996	61.925	1.00	49.26
ATOM	2195	CZ	ARG	A	268	24.052	23.284	61.786	1.00	50.43
ATOM	2196	NH1	ARG	A	268	25.293	23.726	61.914	1.00	50.57
ATOM	2197	NH2	ARG	A	268	23.091	24.147	61.487	1.00	54.11
ATOM	2198	N	PHE	A	269	28.858	19.987	59.621	1.00	36.52
ATOM	2199	CA	PHE	A	269	29.717	20.935	58.938	1.00	35.76
ATOM	2200	C	PHE	A	269	30.059	20.521	57.498	1.00	35.94
ATOM	2201	O	PHE	A	269	30.199	21.370	56.646	1.00	39.34
ATOM	2202	CB	PHE	A	269	31.018	21.117	59.696	1.00	32.56
ATOM	2203	CG	PHE	A	269	31.893	22.188	59.119	1.00	30.04
ATOM	2204	CD1	PHE	A	269	33.037	21.865	58.414	1.00	29.12
ATOM	2205	CD2	PHE	A	269	31.546	23.523	59.261	1.00	32.32
ATOM	2206	CE1	PHE	A	269	33.849	22.857	57.884	1.00	29.89
ATOM	2207	CE2	PHE	A	269	32.337	24.526	58.731	1.00	30.18
ATOM	2208	CZ	PHE	A	269	33.491	24.193	58.030	1.00	34.06
ATOM	2209	N	SER	A	270	30.224	19.228	57.248	1.00	34.50
ATOM	2210	CA	SER	A	270	30.543	18.737	55.913	1.00	34.36
ATOM	2211	C	SER	A	270	29.373	18.941	54.953	1.00	34.34
ATOM	2212	O	SER	A	270	29.558	19.437	53.839	1.00	30.23
ATOM	2213	CB	SER	A	270	30.923	17.262	55.975	1.00	32.60
ATOM	2214	OG	SER	A	270	32.077	17.101	56.773	1.00	37.71
ATOM	2215	N	TYR	A	271	28.176	18.540	55.388	1.00	36.71
ATOM	2216	CA	TYR	A	271	26.929	18.830	54.678	1.00	35.83
ATOM	2217	C	TYR	A	271	26.874	20.295	54.345	1.00	36.60
ATOM	2218	O	TYR	A	271	26.634	20.682	53.213	1.00	37.68
ATOM	2219	CB	TYR	A	271	25.716	18.539	55.563	1.00	38.12
ATOM	2220	CG	TYR	A	271	25.160	17.142	55.497	1.00	34.68
ATOM	2221	CD1	TYR	A	271	25.791	16.096	56.143	1.00	37.80
ATOM	2222	CD2	TYR	A	271	23.981	16.874	54.809	1.00	40.16
ATOM	2223	CE1	TYR	A	271	25.279	14.805	56.102	1.00	39.89
ATOM	2224	CE2	TYR	A	271	23.465	15.582	54.754	1.00	42.27
ATOM	2225	CZ	TYR	A	271	24.114	14.557	55.411	1.00	42.20
ATOM	2226	OH	TYR	A	271	23.612	13.277	55.375	1.00	49.03
ATOM	2227	N	LEU	A	272	27.117	21.112	55.357	1.00	38.95
ATOM	2228	CA	LEU	A	272	26.998	22.553	55.225	1.00	39.72
ATOM	2229	C	LEU	A	272	27.988	23.097	54.212	1.00	40.36
ATOM	2230	O	LEU	A	272	27.638	23.981	53.432	1.00	42.33
ATOM	2231	CB	LEU	A	272	27.178	23.217	56.593	1.00	42.16
ATOM	2232	CG	LEU	A	272	27.040	24.733	56.691	1.00	46.41
ATOM	2233	CD1	LEU	A	272	25.793	25.257	55.955	1.00	48.86
ATOM	2234	CD2	LEU	A	272	27.006	25.141	58.175	1.00	49.08
ATOM	2235	N	ALA	A	273	29.211	22.553	54.198	1.00	36.56
ATOM	2236	CA	ALA	A	273	30.250	23.024	53.281	1.00	34.47
ATOM	2237	C	ALA	A	273	29.931	22.604	51.851	1.00	31.70
ATOM	2238	O	ALA	A	273	30.176	23.341	50.913	1.00	34.20
ATOM	2239	CB	ALA	A	273	31.622	22.490	53.690	1.00	35.73
ATOM	2240	N	VAL	A	274	29.394	21.409	51.697	1.00	31.56
ATOM	2241	CA	VAL	A	274	29.082	20.878	50.381	1.00	34.59
ATOM	2242	C	VAL	A	274	27.909	21.683	49.790	1.00	38.49
ATOM	2243	O	VAL	A	274	27.952	22.053	48.617	1.00	39.12
ATOM	2244	CB	VAL	A	274	28.817	19.341	50.454	1.00	31.94
ATOM	2245	CG1	VAL	A	274	28.213	18.791	49.172	1.00	33.30
ATOM	2246	CG2	VAL	A	274	30.111	18.592	50.765	1.00	31.69
ATOM	2247	N	ILE	A	275	26.908	21.999	50.610	1.00	36.26
ATOM	2248	CA	ILE	A	275	25.726	22.739	50.155	1.00	39.86

ATOM	2249	C	ILE	A	275	26.088	24.160	49.728	1.00 38.34
ATOM	2250	O	ILE	A	275	25.704	24.613	48.665	1.00 39.42
ATOM	2251	CB	ILE	A	275	24.651	22.778	51.277	1.00 41.82
ATOM	2252	CG1	ILE	A	275	24.023	21.400	51.473	1.00 43.45
ATOM	2253	CG2	ILE	A	275	23.552	23.784	50.969	1.00 44.70
ATOM	2254	CD1	ILE	A	275	23.449	21.196	52.861	1.00 45.17
ATOM	2255	N	GLU	A	276	26.827	24.871	50.558	1.00 37.37
ATOM	2256	CA	GLU	A	276	27.189	26.238	50.227	1.00 39.70
ATOM	2257	C	GLU	A	276	28.234	26.289	49.120	1.00 39.46
ATOM	2258	O	GLU	A	276	28.251	27.222	48.305	1.00 41.95
ATOM	2259	CB	GLU	A	276	27.676	26.973	51.476	1.00 42.35
ATOM	2260	CG	GLU	A	276	26.568	27.180	52.502	1.00 48.65
ATOM	2261	CD	GLU	A	276	26.923	28.196	53.583	1.00 55.14
ATOM	2262	OE1	GLU	A	276	26.335	28.108	54.695	1.00 58.67
ATOM	2263	OE2	GLU	A	276	27.787	29.080	53.330	1.00 57.40
ATOM	2264	N	GLY	A	277	29.115	25.294	49.083	1.00 35.14
ATOM	2265	CA	GLY	A	277	30.073	25.188	47.996	1.00 34.64
ATOM	2266	C	GLY	A	277	29.363	24.978	46.668	1.00 32.72
ATOM	2267	O	GLY	A	277	29.753	25.543	45.673	1.00 31.78
ATOM	2268	N	ALA	A	278	28.313	24.165	46.674	1.00 36.31
ATOM	2269	CA	ALA	A	278	27.550	23.852	45.471	1.00 39.36
ATOM	2270	C	ALA	A	278	26.795	25.062	44.966	1.00 43.06
ATOM	2271	O	ALA	A	278	26.734	25.286	43.767	1.00 45.13
ATOM	2272	CB	ALA	A	278	26.583	22.727	45.736	1.00 35.74
ATOM	2273	N	LYS	A	279	26.228	25.840	45.884	1.00 47.70
ATOM	2274	CA	LYS	A	279	25.511	27.067	45.522	1.00 50.45
ATOM	2275	C	LYS	A	279	26.459	28.064	44.865	1.00 50.00
ATOM	2276	O	LYS	A	279	26.076	28.756	43.929	1.00 53.95
ATOM	2277	CB	LYS	A	279	24.831	27.699	46.755	1.00 49.65
ATOM	2278	CG	LYS	A	279	23.598	26.941	47.224	1.00 53.64
ATOM	2279	CD	LYS	A	279	22.857	27.678	48.345	1.00 56.88
ATOM	2280	CE	LYS	A	279	21.838	26.777	49.068	1.00 58.26
ATOM	2281	NZ	LYS	A	279	21.551	27.277	50.453	1.00 59.08
ATOM	2282	N	PHE	A	280	27.695	28.115	45.351	1.00 49.27
ATOM	2283	CA	PHE	A	280	28.699	29.043	44.838	1.00 49.04
ATOM	2284	C	PHE	A	280	29.220	28.642	43.455	1.00 49.80
ATOM	2285	O	PHE	A	280	29.433	29.495	42.603	1.00 49.32
ATOM	2286	CB	PHE	A	280	29.869	29.147	45.826	1.00 50.39
ATOM	2287	CG	PHE	A	280	30.921	30.124	45.415	1.00 49.33
ATOM	2288	CD1	PHE	A	280	30.765	31.478	45.668	1.00 49.83
ATOM	2289	CD2	PHE	A	280	32.067	29.694	44.758	1.00 49.42
ATOM	2290	CE1	PHE	A	280	31.733	32.384	45.274	1.00 48.13
ATOM	2291	CE2	PHE	A	280	33.027	30.595	44.368	1.00 48.06
ATOM	2292	CZ	PHE	A	280	32.863	31.944	44.631	1.00 48.21
ATOM	2293	N	ILE	A	281	29.430	27.347	43.240	1.00 50.12
ATOM	2294	CA	ILE	A	281	29.905	26.840	41.951	1.00 50.40
ATOM	2295	C	ILE	A	281	28.749	26.722	40.939	1.00 55.35
ATOM	2296	O	ILE	A	281	28.971	26.875	39.742	1.00 55.56
ATOM	2297	CB	ILE	A	281	30.633	25.483	42.139	1.00 49.67
ATOM	2298	CG1	ILE	A	281	31.938	25.690	42.912	1.00 48.72
ATOM	2299	CG2	ILE	A	281	30.947	24.833	40.802	1.00 50.91
ATOM	2300	CD1	ILE	A	281	32.411	24.478	43.633	1.00 47.70
ATOM	2301	N	MET	A	282	27.527	26.496	41.438	1.00 60.40
ATOM	2302	CA	MET	A	282	26.324	26.216	40.624	1.00 63.02
ATOM	2303	C	MET	A	282	25.115	27.081	41.102	1.00 62.62
ATOM	2304	O	MET	A	282	25.174	28.305	41.019	1.00 61.79
ATOM	2305	CB	MET	A	282	25.995	24.704	40.658	1.00 65.42
ATOM	2306	CG	MET	A	282	27.178	23.756	40.371	1.00 67.60

ATOM	2307	SD	MET	A	282	26.819	21.976	40.681	1.00	70.48
ATOM	2308	CE	MET	A	282	26.610	21.357	38.979	1.00	68.57
ATOM	2309	N	GLY	A	283	24.116	26.529	41.557	1.00	60.55
HETATM	2310	MG	MG	A	1282	44.422	-3.071	46.899	1.00	60.24
HETATM	2311	O	HOH	Z	1	22.845	21.799	47.502	1.00	40.64
HETATM	2312	O	HOH	Z	2	15.323	16.826	46.375	1.00	49.94
HETATM	2313	O	HOH	Z	3	15.473	19.469	45.770	1.00	50.98
HETATM	2314	O	HOH	Z	4	22.424	19.648	43.271	1.00	45.79
HETATM	2315	O	HOH	Z	5	15.775	14.423	51.730	1.00	55.85
HETATM	2316	O	HOH	Z	6	21.510	17.929	46.342	1.00	41.90
HETATM	2317	O	HOH	Z	7	23.215	13.722	50.672	1.00	52.16
HETATM	2318	O	HOH	Z	8	21.609	15.105	67.182	1.00	55.05
HETATM	2319	O	HOH	Z	9	46.068	-6.909	53.961	1.00	41.54
HETATM	2320	O	HOH	Z	10	46.376	-3.583	45.594	1.00	48.83
HETATM	2321	O	HOH	Z	11	37.768	1.718	44.042	1.00	47.36
HETATM	2322	O	HOH	Z	12	33.307	2.262	54.833	1.00	33.08
HETATM	2323	O	HOH	Z	13	33.935	-1.788	53.445	1.00	53.29
HETATM	2324	O	HOH	Z	14	34.355	-4.241	57.338	1.00	37.80
HETATM	2325	O	HOH	Z	15	39.461	-5.904	60.525	1.00	54.82
HETATM	2326	O	HOH	Z	16	65.218	12.046	62.590	1.00	53.16
HETATM	2327	O	HOH	Z	17	43.693	-3.408	55.400	1.00	30.74
HETATM	2328	O	HOH	Z	18	44.621	-4.890	63.128	1.00	44.34
HETATM	2329	O	HOH	Z	19	50.688	-6.839	63.918	1.00	46.36
HETATM	2330	O	HOH	Z	20	53.338	-0.323	66.457	1.00	42.76
HETATM	2331	O	HOH	Z	21	58.119	-5.709	64.896	1.00	47.61
HETATM	2332	O	HOH	Z	22	49.949	29.097	63.293	1.00	46.85
HETATM	2333	O	HOH	Z	23	59.882	1.566	67.930	1.00	52.42
HETATM	2334	O	HOH	Z	24	54.549	27.023	69.066	1.00	53.35
HETATM	2335	O	HOH	Z	25	54.922	7.670	60.300	1.00	25.86
HETATM	2336	O	HOH	Z	26	55.413	8.114	69.236	1.00	55.54
HETATM	2337	O	HOH	Z	27	54.620	16.584	67.844	1.00	33.49
HETATM	2338	O	HOH	Z	28	48.736	6.328	65.214	1.00	47.76
HETATM	2339	O	HOH	Z	29	48.168	5.412	67.908	1.00	51.62
HETATM	2340	O	HOH	Z	30	49.368	13.438	69.668	1.00	49.93
HETATM	2341	O	HOH	Z	31	53.010	10.206	70.372	1.00	50.44
HETATM	2342	O	HOH	Z	32	45.701	11.273	61.044	1.00	32.29
HETATM	2343	O	HOH	Z	33	47.764	14.051	63.278	1.00	28.70
HETATM	2344	O	HOH	Z	34	48.591	33.053	61.075	1.00	54.29
HETATM	2345	O	HOH	Z	35	59.212	38.307	51.294	1.00	36.89
HETATM	2346	O	HOH	Z	36	42.763	3.390	58.521	1.00	24.82
HETATM	2347	O	HOH	Z	37	49.100	-0.663	58.705	1.00	28.91
HETATM	2348	O	HOH	Z	38	47.165	-7.209	56.440	1.00	51.31
HETATM	2349	O	HOH	Z	39	47.633	1.624	48.231	1.00	37.22
HETATM	2350	O	HOH	Z	40	46.061	-3.333	48.336	1.00	40.00
HETATM	2351	O	HOH	Z	41	43.327	-0.027	48.387	1.00	50.01
HETATM	2352	O	HOH	Z	42	50.571	-3.228	53.736	1.00	38.96
HETATM	2353	O	HOH	Z	43	53.415	-5.064	53.846	1.00	46.67
HETATM	2354	O	HOH	Z	44	50.046	-0.876	50.397	1.00	49.13
HETATM	2355	O	HOH	Z	45	50.046	3.190	48.165	1.00	53.01
HETATM	2356	O	HOH	Z	46	52.816	2.772	55.478	1.00	31.25
HETATM	2357	O	HOH	Z	47	52.633	2.939	48.418	1.00	39.93
HETATM	2358	O	HOH	Z	48	54.727	4.247	45.978	1.00	57.14
HETATM	2359	O	HOH	Z	49	64.959	6.495	56.895	1.00	52.00
HETATM	2360	O	HOH	Z	50	57.310	-1.724	58.570	1.00	41.45
HETATM	2361	O	HOH	Z	51	35.848	27.712	42.926	1.00	54.37
HETATM	2362	O	HOH	Z	52	50.085	28.801	43.139	1.00	51.13
HETATM	2363	O	HOH	Z	53	60.300	-2.855	54.748	1.00	41.74
HETATM	2364	O	HOH	Z	54	58.529	-1.199	50.605	1.00	57.32

HETATM	2365	O	HOH	Z	55	45.923	2.979	54.926	1.00 25.76
HETATM	2366	O	HOH	Z	56	44.320	2.706	48.454	1.00 38.15
HETATM	2367	O	HOH	Z	57	36.785	4.672	45.000	1.00 35.08
HETATM	2368	O	HOH	Z	58	43.473	1.757	45.584	1.00 56.90
HETATM	2369	O	HOH	Z	59	41.338	8.084	41.254	1.00 53.25
HETATM	2370	O	HOH	Z	60	30.433	10.290	37.115	1.00 42.75
HETATM	2371	O	HOH	Z	61	31.585	8.142	44.010	1.00 42.88
HETATM	2372	O	HOH	Z	62	34.418	5.931	43.460	1.00 45.06
HETATM	2373	O	HOH	Z	63	34.334	8.999	43.667	1.00 24.43
HETATM	2374	O	HOH	Z	64	42.041	11.533	35.987	1.00 56.05
HETATM	2375	O	HOH	Z	65	41.705	15.415	39.845	1.00 40.42
HETATM	2376	O	HOH	Z	66	28.818	7.428	45.833	1.00 48.27
HETATM	2377	O	HOH	Z	67	43.334	9.923	40.587	1.00 41.88
HETATM	2378	O	HOH	Z	68	45.358	15.279	44.879	1.00 20.78
HETATM	2379	O	HOH	Z	69	46.213	7.669	42.907	1.00 45.16
HETATM	2380	O	HOH	Z	70	45.006	13.333	58.392	1.00 35.27
HETATM	2381	O	HOH	Z	71	53.156	12.001	58.616	1.00 21.44
HETATM	2382	O	HOH	Z	72	62.274	13.778	61.807	1.00 24.83
HETATM	2383	O	HOH	Z	73	62.055	17.949	63.823	1.00 40.42
HETATM	2384	O	HOH	Z	74	59.258	11.404	67.333	1.00 33.68
HETATM	2385	O	HOH	Z	75	54.744	10.535	60.395	1.00 20.48
HETATM	2386	O	HOH	Z	76	57.163	6.768	59.559	1.00 25.08
HETATM	2387	O	HOH	Z	77	63.881	8.324	47.356	1.00 49.33
HETATM	2388	O	HOH	Z	78	54.853	6.749	43.141	1.00 51.35
HETATM	2389	O	HOH	Z	79	59.012	7.907	42.952	1.00 48.18
HETATM	2390	O	HOH	Z	80	56.575	6.893	49.289	1.00 32.44
HETATM	2391	O	HOH	Z	81	52.021	8.983	43.755	1.00 42.49
HETATM	2392	O	HOH	Z	82	53.922	16.287	40.345	1.00 39.26
HETATM	2393	O	HOH	Z	83	59.899	11.559	42.572	1.00 49.40
HETATM	2394	O	HOH	Z	84	56.645	15.814	45.124	1.00 27.98
HETATM	2395	O	HOH	Z	85	42.223	29.114	66.968	1.00 57.11
HETATM	2396	O	HOH	Z	86	51.099	26.686	63.307	1.00 33.40
HETATM	2397	O	HOH	Z	87	50.936	27.431	66.552	1.00 29.14
HETATM	2398	O	HOH	Z	88	43.726	25.589	64.518	1.00 43.95
HETATM	2399	O	HOH	Z	89	43.533	20.290	68.698	1.00 42.90
HETATM	2400	O	HOH	Z	90	45.850	20.417	75.681	1.00 50.53
HETATM	2401	O	HOH	Z	91	53.075	16.450	69.664	1.00 32.27
HETATM	2402	O	HOH	Z	92	45.205	18.875	73.394	1.00 48.02
HETATM	2403	O	HOH	Z	93	56.319	20.734	67.582	1.00 34.40
HETATM	2404	O	HOH	Z	94	54.149	27.029	62.968	1.00 41.16
HETATM	2405	O	HOH	Z	95	59.431	20.656	66.113	1.00 30.86
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HETATM	2407	O	HOH	Z	97	55.919	29.254	59.193	1.00 50.97
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HETATM	2413	O	HOH	Z	103	60.616	34.916	57.253	1.00 39.66
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HETATM	2415	O	HOH	Z	105	68.398	28.837	52.842	1.00 34.34
HETATM	2416	O	HOH	Z	106	63.996	35.732	55.676	1.00 42.07
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HETATM	2418	O	HOH	Z	108	69.301	26.294	58.726	1.00 45.15
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HETATM	2421	O	HOH	Z	111	62.227	10.934	59.636	1.00 26.45
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HETATM	2440	O	HOH Z	130	58.628	21.386	40.694	1.00 42.73
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HETATM	2445	O	HOH Z	135	44.797	27.868	71.294	1.00 45.84
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HETATM	2448	O	HOH Z	138	35.848	19.568	69.764	1.00 50.41
HETATM	2449	O	HOH Z	139	37.851	21.728	66.890	1.00 36.19
HETATM	2450	O	HOH Z	140	30.783	23.866	66.937	1.00 50.34
HETATM	2451	O	HOH Z	141	33.726	27.401	67.001	1.00 58.33
HETATM	2452	O	HOH Z	142	28.915	24.727	61.642	1.00 47.60
HETATM	2453	O	HOH Z	143	33.769	31.236	57.483	1.00 46.31
HETATM	2454	O	HOH Z	144	34.891	27.864	57.438	1.00 42.43
HETATM	2455	O	HOH Z	145	46.252	29.134	45.085	1.00 41.22
HETATM	2456	O	HOH Z	146	33.519	21.089	41.828	1.00 28.37
HETATM	2457	O	HOH Z	147	36.513	25.357	42.533	1.00 28.71
HETATM	2458	O	HOH Z	148	44.082	21.238	41.779	1.00 24.55
HETATM	2459	O	HOH Z	149	44.511	30.853	43.295	1.00 52.96
HETATM	2460	O	HOH Z	150	37.321	31.395	45.097	1.00 57.97
HETATM	2461	O	HOH Z	151	50.444	27.054	41.455	1.00 46.22
HETATM	2462	O	HOH Z	152	50.470	23.304	40.354	1.00 46.12
HETATM	2463	O	HOH Z	153	49.473	17.014	44.938	1.00 22.23
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HETATM	2465	O	HOH Z	155	46.743	15.157	42.567	1.00 28.06
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HETATM	2467	O	HOH Z	157	44.029	19.607	35.637	1.00 33.31
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HETATM	2470	O	HOH Z	160	52.916	22.239	37.026	1.00 55.49
HETATM	2471	O	HOH Z	161	45.869	13.974	60.909	1.00 34.41
HETATM	2472	O	HOH Z	162	48.083	16.068	66.708	1.00 33.89
HETATM	2473	O	HOH Z	163	43.023	14.129	61.953	1.00 53.88
HETATM	2474	O	HOH Z	164	38.756	19.276	65.202	1.00 36.58
HETATM	2475	O	HOH Z	165	39.907	13.260	59.270	1.00 40.54
HETATM	2476	O	HOH Z	166	36.800	15.818	59.356	1.00 38.21
HETATM	2477	O	HOH Z	167	30.756	21.819	41.946	1.00 52.32
HETATM	2478	O	HOH Z	168	26.321	18.194	36.951	1.00 49.33
HETATM	2479	O	HOH Z	169	28.298	20.489	35.444	1.00 47.56
HETATM	2480	O	HOH Z	170	34.060	21.200	39.322	1.00 37.57

```
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HETATM 2484  O   HOH Z 174      29.883  11.426  33.922  1.00 37.75
HETATM 2485  O   HOH Z 175      30.389  15.363  32.808  1.00 37.18
HETATM 2486  O   HOH Z 176      25.224  10.459  26.647  1.00 58.79
HETATM 2487  O   HOH Z 177      26.104  10.611  35.365  1.00 35.22
HETATM 2488  O   HOH Z 178      19.926   9.452  39.387  1.00 55.25
HETATM 2489  O   HOH Z 179      19.723  16.723  39.659  1.00 52.43
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HETATM 2493  O   HOH Z 183      21.411  12.400  47.935  1.00 51.82
HETATM 2494  O   HOH Z 184      26.338   9.343  45.940  1.00 38.29
HETATM 2495  O   HOH Z 185      28.937   4.006  49.860  1.00 46.67
HETATM 2496  O   HOH Z 186      35.592   1.182  45.532  1.00 43.21
HETATM 2497  O   HOH Z 187      42.181  12.293  59.682  1.00 44.13
HETATM 2498  O   HOH Z 188      40.677  11.462  62.985  1.00 35.66
HETATM 2499  O   HOH Z 189      34.830   8.329  59.655  1.00 45.13
HETATM 2500  O   HOH Z 190      39.290   9.584  68.605  1.00 52.23
HETATM 2501  O   HOH Z 191      29.697  13.317  68.291  1.00 52.85
HETATM 2502  O   HOH Z 192      24.761  18.714  66.413  1.00 59.04
HETATM 2503  O   HOH Z 193      29.424  16.578  68.004  1.00 52.70
HETATM 2504  O   HOH Z 194      28.068  22.230  62.043  1.00 49.54
HETATM 2505  O   HOH Z 195      26.825  29.550  56.806  1.00 54.77
END
```

TABLE 2

All atoms as in Table 1 (incorporated herein by reference) except for the following six changes:

1) Delete lines for Atom 1770-1793

2) Replace with:

```
ATOM   1770  N   CYS A 215      45.982  16.650  59.851  1.00 21.29
ATOM   1771  CA  CYS A 215      45.553  17.584  60.885  1.00 21.43
ATOM   1772  C   CYS A 215      46.211  17.303  62.215  1.00 24.05
ATOM   1773  O   CYS A 215      47.355  16.913  62.307  1.00 22.32
ATOM   1774  CB  CYS A 215      44.037  17.520  61.166  1.00 22.73
ATOM   1775  SG  CYS A 215      43.916  18.029  62.855  1.00 30.96
ATOM   1776  N   SER A 216      45.432  17.553  63.271  1.00 28.96
ATOM   1777  CA  SER A 216      45.887  17.111  64.593  1.00 33.95
ATOM   1778  C   SER A 216      45.405  15.709  64.892  1.00 38.49
ATOM   1779  O   SER A 216      44.329  15.318  64.490  1.00 38.68
ATOM   1780  CB  SER A 216      45.451  18.035  65.735  1.00 34.57
ATOM   1781  OG  SER A 216      45.116  19.351  65.362  1.00 36.62
```

3) Renumber following atoms (from ALA 217) accordingly.

4) Insert following line after new ATOM 2297 (old ATOM 2309):

```
TER    2298      GLY A 283
```

5) Insert following Header to PDB file:

```
LINK        MG   MG        A1282        O   HOH Z 106     1555   4546
LINK        MG   MG        A1282        O   HOH Z  10     1555   1555
LINK        MG   MG        A1282        O   HOH Z  40     1555   1555
LINK        SG   CYS       A 215        N   SER A 216     1555   1555
```

6) Insert following Footer instead of END line:

```
CONECT 1775 1776
CONECT 1776 1775
CONECT 2299 2405 2309 2339
CONECT 2309 2299
CONECT 2339 2299
CONECT 2405 2299
MASTER    498    0    1    9   11    0    1    6 2493    1    6
25
END
```

SEQUENCE LISTING

<110> Astex Technology Limited
Carr, Robin A.E.
Jhoti, Harren
Williams, Glyn
Wallis, Nicola G.
van Montfort, Robert L. M.
Tisi, Dominic J.G.
Congreve, Miles S.

<120> PHARMACEUTICAL COMPOUNDS

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<151> 2003-04-02

<150> US 60/468,543

<151> 2003-05-07

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CLAIMS

1. Isolated sulfenyl amide cysteine-containing protein, or a homologue, allelic form, species variant, derivative or mutein thereof.

2. Isolated protein sulfenyl amide characterised by the HC(X5)R signature motif, or a homologue, allelic form, species variant, derivative or mutein thereof.

3. Isolated PTP sulfenyl amide, or a homologue, allelic form, species variant, derivative or mutein thereof.

4. A process for screening for an inhibitor of a protein (such as PTP) capable of forming a sulfenyl amide as defined in any one of claims 1 to 3, which process comprises the steps of: (a) providing a sulfenyl amide of the protein (e.g. PTP sulfenyl amide) (or a homologue, allelic form, species variant, derivative or mutein thereof); (b) contacting the sulfenyl amide of step (a) with a test compound; and (c) determining whether the test compound binds to the sulfenyl amide.

5. A process for producing an inhibitor of a protein (such as PTP) capable of forming a sulfenyl amide as defined in any one of claims 1 to 3, which process comprises the steps of: (a) providing a sulfenyl amide of the protein (e.g. PTP sulfenyl amide) (or a homologue, allelic form, species variant, derivative or mutein thereof); (b) contacting the sulfenyl amide of step (a) with a test compound; (c) determining whether the test compound binds to the sulfenyl amide; and (d) identifying the test compound as an inhibitor (e.g. a PTP inhibitor) on the basis of its ability to prevent or inhibit the reductive activation of the sulfenyl amide (e.g. PTP sulfenyl amide) to active protein (e.g. PTP).

6. The process of claim 5 wherein at least two chemically distinct test compounds are identified in step (d) and wherein the process further comprises the step of linking two or more of the chemically distinct compounds to produce a multimeric inhibitor.

7. The process of claim 5 or claim 6 for producing a pharmaceutical composition further comprising the step of: (e) incorporating the inhibitor identified in step (d) into a pharmaceutical excipient.

8. The sulfenyl amide of any one of claims 1 to 3 which is suitable for use in the process of any one of claims 4 to 7.

9. A protein (e.g. PTP) inhibitor obtainable by, or obtained by, the process of any one of claims 4 to 6.

10. A pharmaceutical composition obtainable by, or obtained by, the process of claim 7.

11. Use of a protein sulfenyl amide (e.g. PTP sulfenyl amide) for drug screening.

12. The use of a compound for the manufacture of a medicament for the treatment of a disease or condition mediated by protein tyrosine phosphatase, wherein the compound is one that binds to protein tyrosine phosphatase sulfenyl amide to prevent or inhibit conversion of the protein tyrosine phosphatase sulfenyl amide to an active reduced form of the protein tyrosine phosphatase.

13. A method of reducing the activity of a protein tyrosine phosphotase (PTP), the PTP being one which is convertible between an active form and an inactive form, the inactive form being characterised by the presence of a sulfenyl amide moiety formed at the active site of the PTP between the sulphur atom of a cysteine group and a backbone nitrogen atom of a neighbouring amino acid, whereby the sulfenyl amide moiety distorts and inactivates the active site of the PTP and wherein the sulfenyl amide moiety is disruptible to restore the inactivate form of the PTP to the active form thereof;

which method comprises inhibiting disruption of the sulfenyl amide moiety, or modifying the sulfenyl amide moiety to prevent restoration of the inactive form of the PTP to the active form.

14. A method according to claim 13 wherein the sulfenyl amide moiety is disruptible by reaction with a reducing agent to restore the inactivate form of the PTP to the active form thereof.

15. A method according to claim 13 or claim 14 wherein the sulfenyl amide moiety is disruptible to regenerate the cysteine group.

16. A method according to claim any one of claims 13 to 15 which comprises inhibiting disruption of the sulfenyl amide moiety by means of a ligand that binds to the inactivated active site of the PTP.

17. A method according to any one of claims 13 to 15 which comprises modifying the sulfenyl amide moiety to prevent restoration of the inactive form of the PTP to the active form.

18. A method according to claim 17 which comprises reversibly modifying the sulfenyl amide moiety.

19. A method according to claim 17 which comprises irreversibly modifying the sulfenyl amide moiety.

20. A method according to any one of claims 17 to 19 in which the sulfenyl amide moiety is modified by reaction with a nucleophilic ligand.

21. A method according to claim 20 wherein the sulfenyl amide moiety is modified by reaction with a nucleophilic ligand having a nucleophilic group that will react with the sulfenyl amide moiety, and a binding region for binding to the PTP sulfenyl amide in the region of the sulfenyl amide moiety.

22. A method according to claim 21 wherein the nucleophilic group is selected from the group consisting of a thiol, disulfane, primary thioamide, secondary thioamide, primary thiourea, secondary thiourea, primary amine, secondary amine, primary hydrazine, secondary hydrazine, primary hydrazide, secondary hydrazide, primary hydrazone, secondary hydrazone,

primary amide, secondary amide, primary urea, secondary urea, primary sulfonamide, secondary sulfonamide, 5-membered ring heterocycle containing NH, alcohol, hydroxylamine, oxime, hydroxamic acid, carboxylic acid (preferably other than an oxalamic acid), sulfoxide, sulfate and a nitrone.

23. A method of identifying by rational drug design a compound capable of reducing the level of activity of a protein tyrosine phosphate (PTP) in a cellular environment, the PTP being one which is convertible in a cellular environment between an active form and an inactive form, the inactive form being characterised by the presence of a sulfenyl amide moiety formed at the active site of the PTP between the sulphur atom of a cysteine group and a backbone nitrogen atom of a neighbouring amino acid;
which method comprises:
(a) designing a ligand that will (i) bind to the active site in the region of the sulfenyl amide moiety to inhibit conversion of the inactive form back to the active form, or (ii) modify the sulfenyl amide moiety to inhibit conversion of the inactive form of the PTP to the active form;
(b) synthesizing the ligand; and
(c) determining whether the ligand reduces the level of activity of a protein tyrosine phosphate (PTP) in a cellular environment.

24. A method according to claim 23 wherein the PTP is PTP1B and the ligand is one which is capable of binding to the sulfenyl amide PTP1B at a binding site as defined in any one of claims 52 to 65

25. A method according to any one of the preceding claims wherein the protein tyrosine phosphatase is characterised by a signature sequence of the formula: (I/V)HCXAGXXR(S/T/G) at a catalytic site thereof wherein the amino acid C is cysteine 215, and wherein the sulfenyl amide moiety is formed between the sulphur atom of cysteine 215 and a backbone nitrogen atom of a neighbouring amino acid.

26. A crystal of sulfenyl amide protein tyrosine phosphatase 1B.

27. A crystal of sulfenyl amide protein tyrosine phosphatase 1B having a Unit cell dimensions: a = 87.686 Å, b = 87.686 Å, c = 103.721 Å, $\alpha = 90.00°$, $\beta = 90.00°$, $\gamma = 120.00°$ and a space group: $P3_1 2 1$.

28. A crystal of sulfenyl amide protein tyrosine phosphatase 1B having a resolution better than, i.e. numerically lower than, 3.0 Å.

29. A crystal of sulfenyl amide protein tyrosine phosphatase 1B having the structure defined by the coordinates of Table 1 or Table 2 ± root mean square deviation from the Cα atoms of not more than 1.5Å.

30. A method of homology modeling comprising the steps of: (a) aligning a representation of an amino acid sequence of a target sulfenyl amide protein tyrosine phosphatase protein of unknown three-dimensional structure with the amino acid sequence of the sulfenyl amide protein tyrosine phosphatase 1B of Table 1 or Table 2 to match homologous regions of the amino acid sequences; (b) modeling the structure of the matched homologous regions of said target sulfenyl amide protein tyrosine phosphatase of unknown structure on the corresponding regions of the sulfenyl amide protein tyrosine phosphatase 1B structure as defined by the coordinates of Table 1 or Table 2 ± root mean square deviation from the Cα atoms of not more than 1.5Å; and (c) determining a conformation (e.g. so that favorable interactions are formed within the target sulfenyl amide protein tyrosine phosphatase of unknown structure and/or so that a low energy conformation is formed) for said target sulfenyl amide protein tyrosine phosphatase of unknown structure which substantially preserves the structure of said matched homologous regions.

31. A method according to claim 30 wherein one or all of steps (a) to (c) are performed by computer modeling.

32. A method for determining the structure of a protein, which method comprises; providing the co-ordinates of Table 1 or Table 2 ± root mean square deviation from the Cα atoms of not more than 1.5Å, and either (a)

positioning the co-ordinates in the crystal unit cell of said protein so as to provide a structure for said protein or (b) assigning NMR spectra peaks of said protein by manipulating the coordinates of Table 1 or Table 2.

33. A method according to claim 32 wherein the co-ordinates of Table 1 or Table 2 ± root mean square deviation from the Cα atoms of not more than 1.5Å are used to solve the structure of a target sulfenyl amide protein tyrosine phosphatase, particularly homologues of sulfenyl amide protein tyrosine phosphatase 1B for example PTP-α, T-cell PTP, or LAR.

34. A system, particularly a computer system, the system containing either (a) atomic coordinate data according to Table 1 or Table 2 ± root mean square deviation from the Cα atoms of not more than 1.5Å, said data defining the three-dimensional structure of sulfenyl amide protein tyrosine phosphatase 1B or at least selected coordinates thereof; (b) structure factor data (where a structure factor comprises the amplitude and phase of the diffracted wave) for sulfenyl amide protein tyrosine phosphatase 1B, said structure factor data being derivable from the atomic coordinate data of Table 1 or Table 2 ± root mean square deviation from the Cα atoms of not more than 1.5Å; (c) atomic coordinate data of a target sulfenyl amide protein tyrosine phosphatase protein generated by homology of the target based on the data of Table 1 or Table 2 ± root mean square deviation from the Cα atoms of not more than 1.5Å; (d) atomic coordinate data of a target sulfenyl amide protein tyrosine phosphatase protein generated by interpreting X-ray crystallographic data or NMR data by reference to the data of Table 1 or Table 2 ± root mean square deviation from the Cα atoms of not more than 1.5Å; or (e) structure factor data derivable from the atomic coordinate data of (c) or (d).

35. A computer-readable storage medium, comprising a data storage material encoded with computer readable data, wherein the data are defined by all or a portion (e.g. selected coordinates as defined herein) of the structure coordinates of sulfenyl amide protein tyrosine phosphatase 1B of Table 1 or

Table 2 ± root mean square deviation from the Cα atoms of not more than 1.5Å, or a homologue of sulfenyl amide protein tyrosine phosphatase 1B, wherein said homologue comprises backbone atoms that have a root mean square deviation from the backbone atoms (nitrogen-carbon$_\alpha$-carbon) of Table 1 or Table 2 of not more than 1.5 Å.

36. A computer-readable data storage medium comprising a data storage material encoded with a first set of computer-readable data comprising a Fourier Transform of at least a portion (e.g. selected coordinates as defined herein) of the structural coordinates for sulfenyl amide protein tyrosine phosphatase 1B according to Table 1 or Table 2 ± root mean square deviation from the Cα atoms of not more than 1.5Å; which, when combined with a second set of machine readable data comprising an X-ray diffraction pattern of a molecule or molecular complex of unknown structure, using a machine programmed with the instructions for using said first set of data and said second set of data, can determine at least a portion of the structure coordinates corresponding to the second set of machine readable data.

37. Computer readable media with at least one of: (a) atomic coordinate data according to Table 1 or Table 2 ± root mean square deviation from the Cα atoms of not more than 1.5Å recorded thereon, said data defining the three-dimensional structure of sulfenyl amide protein tyrosine phosphatase 1B, or at least selected coordinates thereof; (b) structure factor data for sulfenyl amide protein tyrosine phosphatase 1B recorded thereon, the structure factor data being derivable from the atomic coordinate data of Table 1 or Table 2 ± root mean square deviation from the Cα atoms of not more than 1.5Å; (c) atomic coordinate data of a target sulfenyl amide protein tyrosine phosphatase protein generated by homology modeling of the target based on the data of Table 1 or Table 2 ± root mean square deviation from the Cα atoms of not more than 1.5Å; (d) atomic coordinate data of a sulfenyl amide protein tyrosine phosphatase 1B-ligand complex or a sulfenyl amide protein tyrosine phosphatase 1B homologue or analogue generated by interpreting X-ray crystallographic data or NMR data by reference to the data of Table 1

or Table 2 ± root mean square deviation from the Cα atoms of not more than 1.5Å; and (e) structure factor data derivable from the atomic coordinate data of (c) or (d).

38. A method of providing data for generating structures and/or performing rational drug design for sulfenyl amide protein tyrosine phosphatase 1B, sulfenyl amide protein tyrosine phosphatase 1B homologues or analogues, complexes of sulfenyl amide protein tyrosine phosphatase 1B with a candidate modulator, or complexes of sulfenyl amide protein tyrosine phosphatase 1B homologues or analogues with candidate modulators, the method comprising:

(i) establishing communication with a remote device containing computer-readable data comprising at least one of: (a) atomic coordinate data according to Table 1 or Table 2 ± root mean square deviation from the Cα atoms of not more than 1.5Å, said data defining the three-dimensional structure of sulfenyl amide protein tyrosine phosphatase 1B, at least one sub-domain of the three-dimensional structure of sulfenyl amide protein tyrosine phosphatase 1B, or the coordinates of a portion of atoms of sulfenyl amide protein tyrosine phosphatase 1B; (b) structure factor data for sulfenyl amide protein tyrosine phosphatase 1B, said structure factor data being derivable from the atomic coordinate data of Table 1 or Table 2 ± root mean square deviation from the Cα atoms of not more than 1.5Å; (c) atomic coordinate data of a target sulfenyl amide protein tyrosine phosphatase 1B homologue or analogue generated by homology modeling of the target based on the data of Table 1 or Table 2 ± root mean square deviation from the Cα atoms of not more than 1.5Å; (d) atomic coordinate data of a protein generated by interpreting X-ray crystallographic data or NMR data by reference to the data of Table 1 or Table 2 ± root mean square deviation from the Cα atoms of not more than 1.5Å; and (e) structure factor data derivable from the atomic coordinate data of (c) or (d); and

(ii) receiving said computer-readable data from said remote device.

39. A computer-based method of rational drug design which comprises:

providing the structure of the PTP1b sulfenyl amide as defined by the coordinates of Table 1 or Table 2 ± root mean square deviation from the Cα atoms of not more than 1.5Å;

providing the structure of a candidate modulator molecule; and

fitting the structure of candidate to the structure of the sulfenyl amide of Table 1 or Table 2 ± root mean square deviation from the Cα atoms of not more than 1.5Å.

40. A method of rational drug design which comprises;

providing the structure of the PTP1B sulfenyl amide as defined by the coordinates of Table 1 or Table 2 ± root mean square deviation from the Cα atoms of not more than 1.5Å;

providing the structure of a candidate compound; and

fitting the structure of the candidate compound to the structure of the sulfenyl amide as defined by the coordinates of Table 1 or Table 2 ± root mean square deviation from the Cα atoms of not more than 1.5Å.

41. A method of identifying by rational drug design a compound capable of reducing the level of activity of a protein tyrosine phosphatase (PTP) in a cellular environment, the PTP being one which is convertible in a cellular environment between an active form and an inactive or less active form, the inactive form or less active form being characterised by the presence of a sulfenyl amide moiety formed at the active site of the PTP between the sulphur atom of a cysteine group and a backbone nitrogen atom of a neighbouring amino acid;

which method comprises:

(a) designing a ligand that will (i) bind to the active site in the region of the sulfenyl amide moiety to inhibit conversion of the inactive form back to the active form, or (ii) modify the sulfenyl amide moiety to inhibit conversion of the inactive form of the PTP to the active form;

(b) synthesizing the ligand; and

(c) determining whether the ligand reduces the level of activity of a protein tyrosine phosphate (PTP) in a cellular environment.

42. A computer-based method of rational drug design which comprises:

providing the coordinates of at least two atoms of Table 1 or Table 2 of the PTP1B sulfenyl amide ("selected coordinates");

providing the structure of a candidate modulator molecule; and

fitting the structure of candidate to the selected coordinates of the PTP1B sulfenyl amide.

43. A method for determining the structure of a compound bound to sulfenyl amide PTP1B, said method comprising: (a) providing a crystal of sulfenyl amide PTP1b according to the invention; (b) soaking the crystal with said compounds; and (c) determining the structure of said sulfenyl amide PTP1b compound complex by employing the data of Table 1 or Table 2 ± root mean square deviation from the Cα atoms of not more than 1.5Å.

44. A method of inhibiting or preventing the reduction of sulfenyl amide PTB1B to PTB1B in a cellular environment by exposing the PTB1B to a ligand capable of binding to the sulfenyl amide PTB1B in the region of the sulfenyl amide moiety so as to prevent reduction of the sulfenyl amide moiety by an intracellular reducing agent.

45. A method of inhibiting or preventing the reduction of sulfenyl amide PTB1B to PTB1B in a cellular environment by exposing the PTB1B to a ligand capable of binding to the sulfenyl amide PTB1B in the region of the sulfenyl amide moiety, the ligand having a nucleophilic moiety capable of modifying the sulfenyl amide moiety so as to prevent its reduction by an intracellular reducing agent.

46. A method according to claim 44 or claim 45 wherein the ligand is capable of binding to the sulfenyl amide PTP1B at a binding site as defined in any one of claims 52 to 65.

47. A novel compound *per se* that inhibit protein tyrosine phosphatases by interacting with sulfenyl amide PTP to prevent or inhibit conversion of the PTP sulfenyl amide to an active form of the protein tyrosine phosphatase.

48. A compound according to claim 47 for use in medicine, for example for use in the treatment of diseases or conditions mediated by protein tyrosine phosphatase.

49. A compound according to claim 47 or claim 48 which is a non-covalent binding inhibitor that stabilises the sulfenyl-amide protein form.

50. A compound according to claim 47 or claim 48 which binds to and reversibly modifies the sulfenyl-amide form of the protein, e.g. by reacting with the sulfenyl amide moiety, and in so doing, preventing reactivation of the sulfenyl amide PTP by physiological cell cycling.

51. A compound according to claim 47 or claim 48 which binds to and irreversibly modifies the sulfenyl-amide form of the protein, e.g. by reacting irreversibly with the sulfenyl amide moiety, and in so doing, preventing reactivation of the sulfenyl amide PTP by physiological cell cycling.

52. A compound according to any one of claims 47 to 51, which compound is capable of binding to a first binding site of the sulfenyl amide PTP constituted by a groove lined by residues 41-47 of the phosphotyrosine recognition loop, residues 88-90, 115 to 120, residues 179 to 184 of the WPD-loop, residues 215 to 219 of the phosphate-binding cradle, and residues 262-266.

53. A compound according to claim 52 having a molecular shape and charge distribution that enables it to make polar interactions at the first binding site with one or more of:

(1) Lys41
(2) Asn42
(3) Arg45
(4) Tyr46
(5) Arg47
(6) Asn90
(7) Gln115

(8) Lys116
(9) Ser118
(10) Lys120
(11) Trp179
(12) Ser 216
(13) Arg221
(14) Gln262
(15) Thr263
(16) Asp265, and
(17) Gln266;

wherein the amino acid numbering refers to the numbering of the corresponding active form of PTP1B.

54. A compound according to claim 53 having a molecular shape and charge distribution that enables it to make polar interactions with two or more of moieties (1) to (17), more preferably three or more, for example four or more, and more particularly five or more.

55. A compound according to any one of claims 52 to 54 having a molecular shape and charge distribution that enables it to make hydrophobic interactions with one or more of:

(18) Leu88
(19) Pro89
(20) Leu119
(21) Phe182
(22) Gly183
(23) Val184
(24) Ala217
(25) Ile219
(26) the apolar part of Arg221, and
(27) the apolar part of Gln262.

56. A compound according to claim 55 having a molecular shape and charge distribution that enables it to make hydrophobic interactions with two or more of the moieties (18) to (27), more preferably three or more, for example five or more.

57. A compound according to any one of claims 47 to 56, which compound is capable of binding to a second binding site of the sulfenyl amide PTP constituted by a shallow depression defined by residues of the WPD-loop, the pTyr recognition loop and the loop containing residues 28-32.

58. A compound according to claim 57 having a molecular shape and charge distribution that enables it to make polar interactions at the second binding site with one or more of:

(44) Arg24
(14) Gln262
(45) Arg254
(46) Asn 44
(5) Arg47
(4) Tyr46
(1) Lys 41
(47) Lys36
(48) Asp29
(49) Cys32 and
(50) Ser50

59. A compound according to claim 57 or claim 58 having a molecular shape and charge distribution that enables it to make hydrophobic interactions with one or more of:

(51) Leu250
(14) Gln262
(41) Met258
(35) Val49
(4) Tyr46

(39) Gly218
(52) Gly259
(53) Phe52
(42) Leu260
(54) Leu261
(55) Ala35 and
(56) the backbone of Asp48.

60. A compound according to any one of claims 47 to 59, which compound is capable of binding to a third binding site in the form of a cavity having walls formed by Asp48, Val49, Leu83, Gly218, Gly220, Ser222, Arg257, Gly259, Gln262 and the sulfenyl-amide.

61. A compound according to claim 60 having a molecular shape and charge distribution that enables it to make polar interactions at the third binding site with one or more of:
(3) Arg45
(29) Asp48
(30) Ser222
(31) Arg257
(14) Gln262
(33) the protein backbone of one or more of (i) Thr84, (ii) Gly218, (iii) Gly220, (iv) Gly223, (v) Met258, (vi) and Gly259; and
(34) the sulfenyl-amide residue.

62. A compound according to claim 61 having a molecular shape and charge distribution that enables it to make polar interactions at two or more (more preferably three or more, four or more, or five or more) of the residues (3), (29) to (31), (14), (33) and (34).

63. A compound according to any one of claims 60 to 62 having a molecular shape and charge distribution that enables it to make hydrophobic interactions at the third binding site with one or more of:

(35) Val49
(36) Leu83
(37) Gln85
(38) Gly86
(39) Gly218
(40) Gly220
(41) Met258
(42) Leu260 and
(43) the main chain of His214.

64. A compound according to claim 50 or claim 51 which is a nucleophilic ligand, having a nucleophilic group that will react with the sulfenyl amide moiety, and a binding region for binding to the sulfenyl amide PTP in the region of the sulfenyl amide moiety.

65. A compound according to claim 64 wherein the binding region has a molecular shape and charge distribution that enables it to make an interaction with the first and second binding sites as defined in any one of claims 52 to 63.

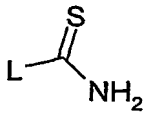
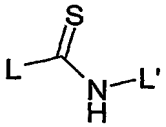
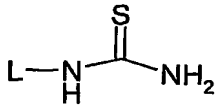
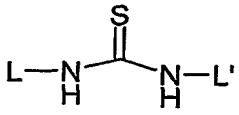
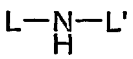
66. A compound according to claim 65 wherein the nucleophilic group contains a heteroatom (e.g. selected from nitrogen, sulphur, oxygen and phosphorus) that is either neutral or negatively charged, and which is capable of reacting with the sulfenyl amide species.

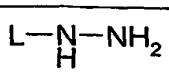
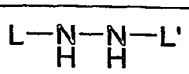
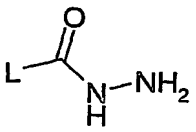
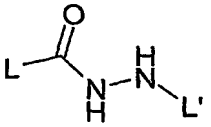
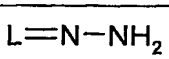
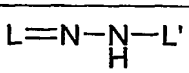
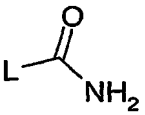
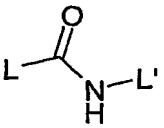
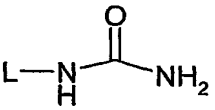
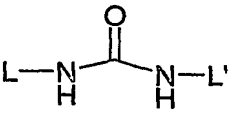
67. A compound according to claim 66 wherein the heteroatom is selected from nitrogen, oxygen and sulfur nucleophiles.

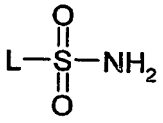
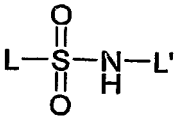
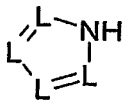
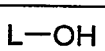
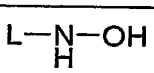
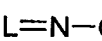
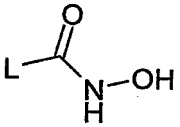
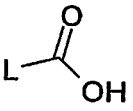
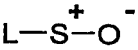
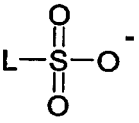
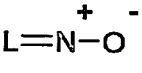
68. A compound according to claim 67 wherein the nucleophilic group is selected from the group consisting of a thiol, disulfane, primary thioamide, secondary thioamide, primary thiourea, secondary thiourea, primary amine, secondary amine, primary hydrazine, secondary hydrazine, primary hydrazide, secondary hydrazide, primary hydrazone, secondary hydrazone, primary amide, secondary amide, primary urea, secondary urea, primary

sulfonamide, secondary sulfonamide, 5-membered ring heterocycle containing NH, alcohol, hydroxylamine, oxime, hydroxamic acid, carboxylic acid (preferably other than an oxalamic acid), sulfoxide, sulfate and a nitrone.

69. A compound according to claim 67 or claim 68 wherein the nucleophile is selected from the group consisting of the nucleophiles set out in Table 3 below, and L is the residue of the compound.

Type of nucleophile	**Structure**	**Name**
Sulphur	L—SH	Thiol
	L—S—SH	Disulfane
		Primary Thioamide
		Secondary Thioamide
		Primary thiourea
		Secondary thiourea
Nitrogen	L—NH_2	Primary amine
		Secondary amine

		Primary Hydrazine
		Secondary Hydrazine
		Primary Hydrazide
		Secondary Hydrazide
		Primary Hydrazone
		Secondary Hydrazone
		Primary amide
		Secondary amide
		Primary urea
		Secondary urea

		Primary Sulfonamide
		Secondary Sulfonamide
		5-membered ring heterocycle containing NH
Oxygen		Alcohol
		Hydroxylamine
		Oxime
		Hydroxamic acid
		Carboxylic acid (preferably not oxalamic acids)
		Sulfoxide
		Sulfate
		Nitrone

70. A compound according to any one of claims 47 to 69 which comprises a scaffold formed from one or more optionally substituted carbocyclic or heterocyclic ring systems, the ring systems and/or the substituents having one or more polar or non-polar moieties for interacting with the first and/or second binding sites.

71. A compound according to claim 70 wherein the carbocyclic and heterocyclic ring systems contain at least one an aromatic ring having from 5 to 12 ring members, more usually from 5 to 10 ring members.

72. A compound according to claim 71 containing a heteroaryl group which is a five membered or six membered monocyclic ring or a bicyclic structure formed from fused five and six membered rings or two fused six membered rings, each ring for example containing up to about four heteroatoms typically selected from nitrogen, sulphur and oxygen, preferably up to 3 heteroatoms, more usually up to 2, for example a single heteroatom.

73. A compound according to claim 72 wherein the heteroaryl group is selected from the group consisting of pyridyl, pyrrolyl, furanyl, thiophenyl, imidazolyl, oxazolyl, oxadiazolyl, oxatriazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, pyrazinyl, pyrimidinyl, triazinyl, triazolyl, tetrazolyl, quinolinyl, isoquinolinyl, benzfuranyl, benzthiophenyl, chromanyl, thiochromanyl, benzimidazolyl, benzoxazolyl, benzisoxazole, benzthiazolyl and benzisothiazole, isobenzofuranyl, isoindolyl, indolizinyl, indolinyl, isoindolinyl, purinyl (e.g., adenine, guanine), indazolyl, benzodioxolyl, chromenyl, isochromenyl, chroman, isochromanyl, benzodioxanyl, quinolizinyl, benzoxazinyl, benzodiazinyl, pyridopyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, phthalazinyl, naphthyridinyl and pteridinyl.

74. A compound according to claim 71 containing at least one carbocyclic aryl group selected from the group consisting of phenyl, naphthyl, indenyl, and tetrahydronaphthyl.

75. A compound according to claim 70 containing at least one non-aromatic heterocyclic group having from 3 to 12 ring members, more usually 5 to 10 ring members.

76. A compound according to claim 75 wherein the non-aromatic heterocyclic group is monocyclic or bicyclic, and is optionally selected from the group consisting of cyclic ether moieties (e.g as in tetrahydrofuran and dioxane), cyclic thioether moieties (e.g. as in tetrahydrothiophene), cyclic amine moieties (e.g. as in pyrrolidine), cyclic sulphones (e.g. as in sulfolane and sulfolene)), cyclic sulphoxides, cyclic sulphonamides and combinations thereof.

77. A compound according to claim 76 wherein the non-aromatic heterocyclic group is selected from the group consisting of morpholine, piperidine, pyrrolidine, pyrrolidone, tetrahydrofuran, tetrahydrothiophene, dioxan, tetrahydropyran, imidazoline, imidazolidinone, oxazoline, thiazoline, piperazine, and N-alkyl piperazines such as N-methyl piperazine.

78. A compound according to any one of claims 70 to 77 wherein the carbocyclic and heterocyclic groups are substituted by one or more substituent groups selected from halogen, hydroxy, trifluoromethyl, cyano, nitro, carboxy, amino, carbocyclic and heterocyclic groups having from 3 to 12 ring members; a group R^a-R^b wherein R^a is a bond, O, CO, $X^1C(X^2)$, $C(X^2)X^1$, $X^1C(X^2)X^1$, S, SO, SO_2, NR^cR^d, SO_2NR^c or NR^cSO_2; and R^b is selected from hydrogen, carbocyclic and heterocyclic groups having from 3 to 7 ring members, and a C_{1-8} hydrocarbyl group optionally substituted by one or more substituents selected from hydroxy, oxo, halogen, cyano, nitro, amino, mono- or di-C_{1-4} hydrocarbylamino, carbocyclic and heterocyclic groups having from 3 to 12 ring members and wherein one or more carbon atoms of the C_{1-8} hydrocarbyl group may optionally be replaced by O, S, SO, SO_2, NR^c, $X^1C(X^2)$, $C(X^2)X^1$ or $X^1C(X^2)X^1$;

R^c and R^d are the same or different and each is hydrogen or C_{1-4} hydrocarbyl;

X^1 is O, S or NR^c and X^2 is =O, =S or $=NR^c$.

79. A pharmaceutical composition comprising a compound as defined in any one of claims 47 to 78 and a pharmaceutically acceptable excipient.

80. A compound as defined in any one of claims 47 to 78 for use in medicine, for example in the prevention or treatment of a disease state or condition mediated by PTP such as PTP1B.

81. The use of a compound as defined in anyone of claims 47 to 78 for the manufacture of a medicament for the prevention or treatment of a disease state or condition mediated by PTP such as PTP1B.

82. A method for the prevention or treatment of a disease state or condition mediated by PTP such as PTP1B in a patient (e.g. a human patient) in need thereof, which method comprises administering to the patient a therapeutically effective amount of a compound as defined in any one of claim 47 to 78.

83. A use, method, or compound for use as defined in any one claims 80 to 82 wherein the disease state or condition mediated by PTP such as PTP1B is selected from cancer, diabetes, rheumatoid arthritis and hypertension.

84. A three-dimensional representation of a PTP sulfenyl amide or a portion of a PTP sulfenyl amide, which representation comprises all or a portion of the coordinates of Table 1 or Table 2 ± root mean square deviation from the Cα atoms of not more than 1.5Å.

85. The three-dimensional representation of claim 84, which is a model constructed from all or a portion of the coordinates of Table 1 or Table 2 ± root mean square deviation from the Cα atoms of not more than 1.5Å.

86. The model of claim 85 wherein the portion of PTP sulfenyl amide is a binding cavity and the portion of the coordinates of Table 1 or Table 2 ± root mean square deviation from the Cα atoms of not more than 1.5Å

comprise those of atoms defining a binding site within the binding cavity (for example, the "selected coordinates" as defined herein).

87. A three-dimensional representation of a compound, which fits the model of claim 85 or claim 86 ± root mean square deviation from the Cα atoms of not more than 1.5Å.

88. The three-dimensional representation of claim 87, which is a model of the compound.

89. The model of claim 88 wherein the compound is a pharmacophore.

90. The model of any one of claims 85, 86, 88 or 89 which is: (a) a wire-frame model; (b) a chicken-wire model; (c) a ball-and-stick model; (d) a space-filling model; (e) a stick-model; (f) a ribbon model; (g) a snake model; (h) an arrow and cylinder model; (i) an electron density map; (j) a molecular surface model.

91. The model of any one of claims 85, 86, 88, 89 or 90 which is in physical form.

92. The model of any one of claims 85, 86, 88, 89 or 90 which is in electronic form.

93. The model of claim 92, which comprises a graphical image display on a computer screen.

94. A computer-based method for the analysis of the interaction of a molecular structure with a PTP sulfenyl amide structure of the invention, which comprises: (a) providing a PTP sulfenyl amide model as defined in claim 85, 86 or 90 to 93; (b) providing a molecular structure to be fitted to said PTP sulfenyl amide model; and (c) fitting the molecular structure to the PTP sulfenyl amide model to produce a compound model as defined in claim 88, 89 or 90 to 93.

Figure 1

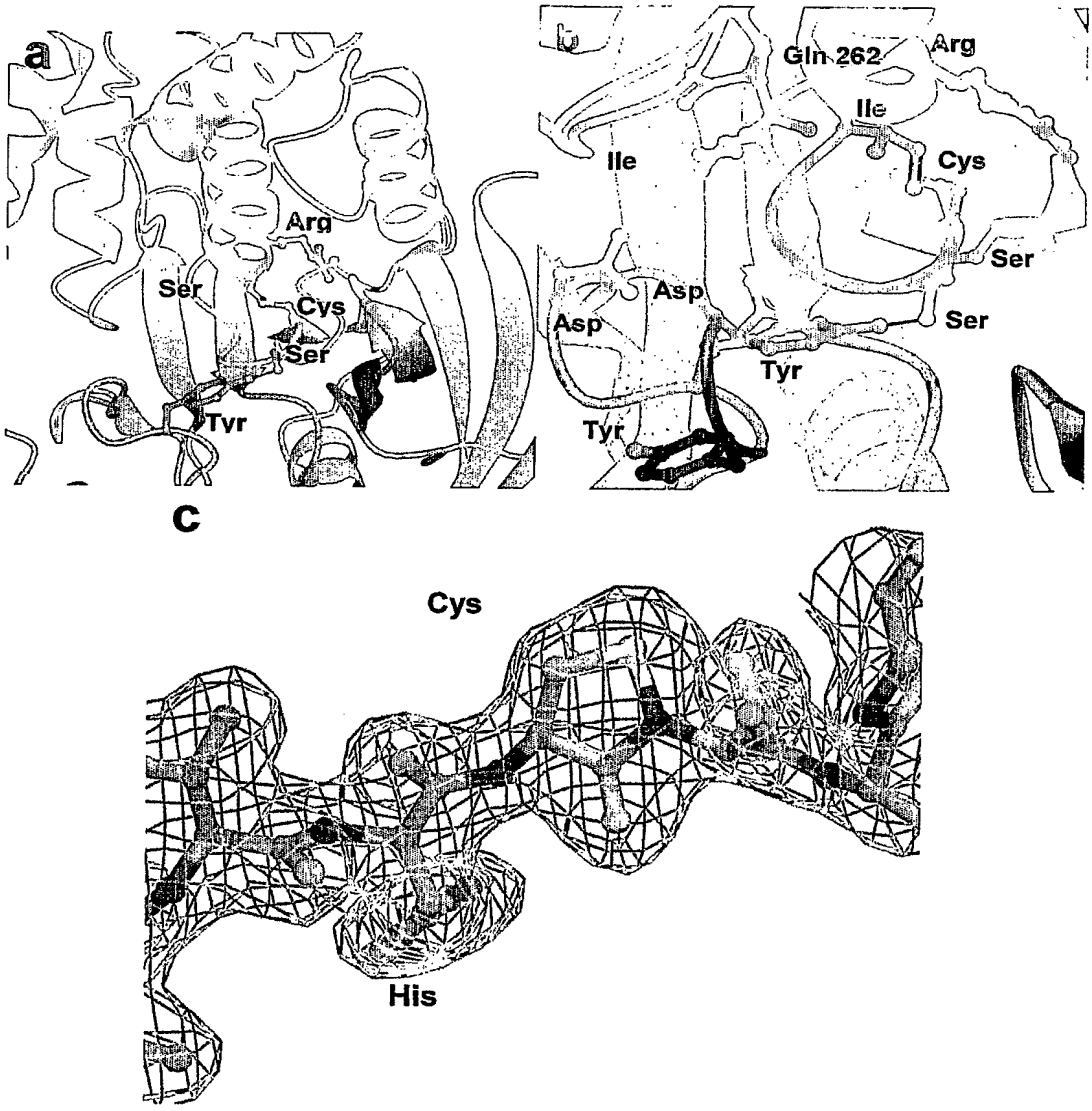


Figure 2

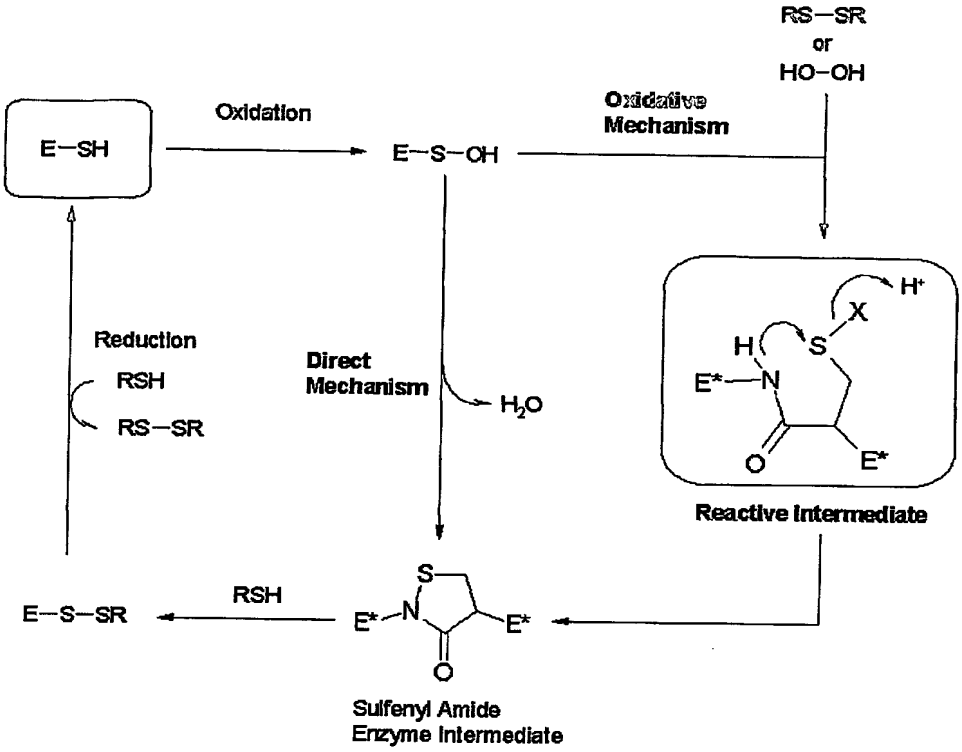


Figure 3